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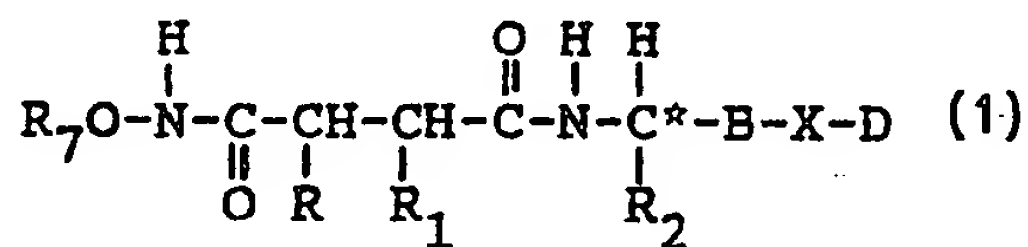
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(54) Title: PEPTIDE DERIVATIVES OF COLLAGENASE INHIBITOR

**(57) Abstract**

This invention is directed to a collagenase inhibitor of formula (1).

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1 PEPTIDE DERIVATIVES OF COLLAGENASE INHIBITOR

 The present invention relates to novel synthetic peptides. More particularly, the invention relates to novel peptides which are useful as inhibitors
5 of mammalian collagenase.

 Collagenases are proteolytic enzymes which initiate the degradation of collagen in vertebrates. In addition to their normal function in the metabolism of connective tissue and wound healing, these endo-
10 proteinases have been implicated in a number of pathological conditions such as joint destruction in rheumatoid arthritis, periodontal disease, corneal ulceration and tumor metastasis.

 Of particular significance is the pathological
15 condition caused by corneal ulceration. Corneal ulceration is caused by different agents. One such cause is alkali burning of the cornea. Although methods of treatment are known, treatment of this condition continues to be a major challenge in ophthalmology.

20 Many therapeutic techniques have been used in an attempt to prevent the sequellae from threatening the integrity of the eye following a chemical injury. These include corticosteroids, heparin, collagenase inhibitors, contact lenses, fibronectin, conjunctival
25 flaps, and corneal transplantation. Recent studies have advocated the use of sodium citrate and sodium ascorbate. Following an ocular alkali burn, a number of degradative processes occur which may result in a corneal ulcer. Several proteases, including
30 collagenases, are released in the chemically injured cornea and account for the ulcerative process. Although the multitude of treatment modalities used in these injuries undoubtedly work by different mechanisms of

1 action, successful management of ocular alkali burns
requires the use of agents which reduce the impact of
collagenase and other proteases upon the cornea.

Heretofore, the efficacy of inhibitors of
5 collagenases for use in human corneal alkali burns is
open to question. Compounds which have been tested
experimentally in animals include acetylcysteine,
cysteine, sodium and calcium EDTA, and penicillamine.
Of these, acetylcysteine which is approved for use as a
10 mucolytic agent, is the only collagenase inhibitor used
clinically in the treatment of human alkali burns. Its
efficacy has yet to be proven in a randomized clinical
trial. Collagenase inhibition by the tetracycline
family of antibiotics has been demonstrated in vitro and
15 systemic tetracycline has recently been shown to inhibit
alkali-induced corneal ulceration in rabbits. Thus, an
adequate inhibitor of collagenase for the treatment of
alkali-induced corneal ulceration has not yet been
developed and is a desired goal in ophthalmology.

Another cause of corneal ulceration is
20 infectious keratitis. Infectious keratitis is the most
common and most serious of the ocular infections. The
organism Pseudomonas aeruginosa (PA) is one of the
leading causes of infectious keratitis. The mainstay of
therapy for infectious keratitis has been antimicrobial
25 agents, but often, even when adequate levels of
antibiotics are delivered, keratitis can progress to
corneal ulceration and perforation. Many organisms,
such as PA, release destructive enzymes which contribute
to the breakdown of the cornea. In addition to enzymes
30 released by the organism, host-derived enzymes, such as
corneal collagenase, are also involved in the
pathogenesis of infectious keratitis. Again, a new

1 treatment for this condition is clearly a major current
need in ophthalmology.

Another area where collagenase inhibitors may
be clinically important is the control of tumor
5 metastasis. Malignant tumor cells differ from other
cancer cells in their ability to spread through the
mammalian body. To do this these cells must destroy
connective tissue by giving off proteolytic enzymes
including collagenases. It is thus postulated that
10 collagenase inhibitors may slow down or even stop
metastasis by inhibiting these enzymes.

Collagenase inhibitors have clinical
significance in the control of certain forms of
dermatitis. It has been found that proteolytic enzymes,
15 including collagenases, are involved in the destruction
of skin tissue. Therefore, the administration of a
collagenase inhibitor would retard and/or prevent these
dermatological diseases by inhibiting these enzymes.

The mechanism of action of mammalian
20 collagenases on the molecular level is fairly well
understood. Tissue collagenases hydrolyze a specific
peptide bond at a single cleavage site on each of the
three collagen chains of triple helical collagen. This
cleavage site is contained within the amino acid
25 sequence Pro-Gln-Gly-Leu-(Ile)-Ala-Gly-Gln-Arg, with
cleavage occurring between glycine 775 and leucine or
isoleucine 776, in Types I, II and III collagen, the
predominant collagen in skin, bone, tendon, dentin,
fascia and cartilage. Type IV collagenase (gelatinase)
30 degrades basement membrane (Type IV) collagen, which may
be important in tumor metastasis. The collagenases are
metallopeptidases which contain an essential zinc at the
active site. The zinc is assumed to function by

1 interactions with the scissile carbonyl of the
substrate, thus facilitating hydrolysis of the peptide
bond.

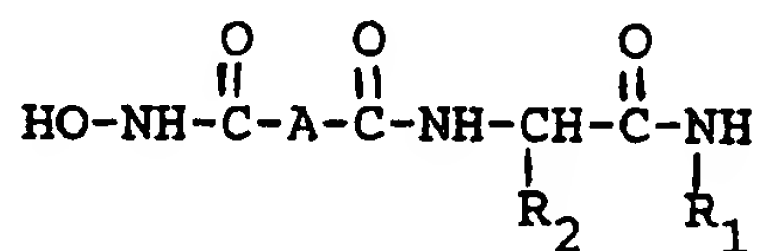
Compounds which coordinate to the zinc active
5 site have the ability to inhibit the activity of the
collagenase. Because of the clinical importance and the
desirability of being able to control these enzymes'
activity, there has been
a widespread effort to design compounds which are
capable of interacting with the enzyme binding site and
10 preventing the enzymes' action. Consequently, there
exists a number of synthetic peptides and chemically
similar compounds which are claimed to have at least
some effect in inhibiting the activity of mammalian
collagenases. Many of these synthetic peptides are
15 constructed so as to mimic the natural amino acid
sequence flanking the collagenase cleavage site. For
example, U.S. Patent No. 4,511,504 describes a number of
carboxyalkyl peptide derivatives said to have inhibitory
activity. U.S. Patent No. 4,263,293 relates to
20 heterocyclic-containing amide compounds, U.S. Patent No.
4,235,885 discloses mercaptoacyl amino acid derivatives,
U.S. Patent No. 4,327,111 teaches N-substituted
mercaptoacyl propionamides, U.S. Patent No. 4,382,081
describes a wide variety of mercapto amino acid
25 derivatives, all of which appear to have some level of
collagenase inhibitory activity. Similarly, U.S. Patent
No. 4,374,765 refers to the use of acyl derivatives of
the peptide Gly-L-Cys-Gly-L-Gln-L-Glu-NH₂. U.S. Patent
No. 4,367,233 refers to thioglycolic acid derivatives,
30 and U.S. Patent No. 4,361,574 teaches alkanoic acid
derivatives which are useful collagenase inhibitors.
U.S. Patent No. 4,595,700 sets forth thiol-based

1 inhibitors. European Patent Application No. 85870005.7
discloses thiopeptolide derivatives as inhibiting
collagenase substrates.

Hydroxamic acid based collagenase inhibitors
5 have also been reported in European Patent Application
Nos. 87102771.0 and 86112386.7.

In U.S. Patent Nos. 4,599,361 and 4,743,587,
Dickens, et al. disclose hydroxamic acid based compounds
of the formula:

10



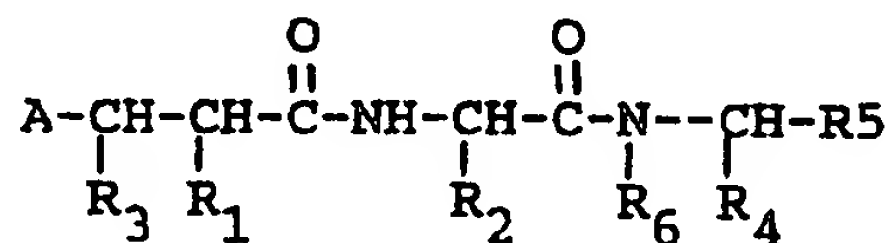
15 wherein R_1 is $\text{C}_1\text{-C}_6$ alkyl;
 R_2 is $\text{C}_1\text{-C}_6$ alkyl, benzyl, benzyloxybenzyl,
($\text{C}_1\text{-C}_6$ alkoxy)benzyl, benzyloxy($\text{C}_1\text{-C}_6$ alkyl) or
hydroxybenzyl;

A is either ($\text{CHR}_3\text{-CHR}_4$), or ($\text{CR}_3\text{-CR}_4$); where
20 R_3 is hydrogen, $\text{C}_1\text{-C}_6$ alkyl, phenyl or phenyl ($\text{C}_1\text{-C}_6$
alkyl), R_4 is hydrogen, $\text{C}_1\text{-C}_6$ alkyl, phenyl ($\text{C}_1\text{-C}_6$
alkyl), cycloalkyl or cycloalkyl ($\text{C}_1\text{-C}_6$ alkyl).

These hydroxamic acid based compounds are
alleged to be collagenase inhibitors.

Handa, et al. in European Patent Application
25 No. 0 236 872 disclose compounds having the formula:

30



wherein A is either HO-NH-CO or HCO-N(OH)- ;
 R_1 is $\text{C}_2\text{-C}_5$ alkyl;

35

1 R_2 is a natural amino acid having a functional group containing amino or carboxy with the proviso that R_2 is not hydrogen or methyl;

5 R_3 is hydrogen, amino, hydroxy, mercapto, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, aryl (C_1-C_6 alkyl), amino (C_1-C_6 alkyl), hydroxy (C_1-C_6 alkyl), mercapto (C_1-C_6 alkyl) or carboxy (C_1-C_6 alkyl), wherein the amino, hydroxy, mercapto and carboxyl groups may be protected by an acylated amino group;

10 R_4 is hydrogen or methyl;

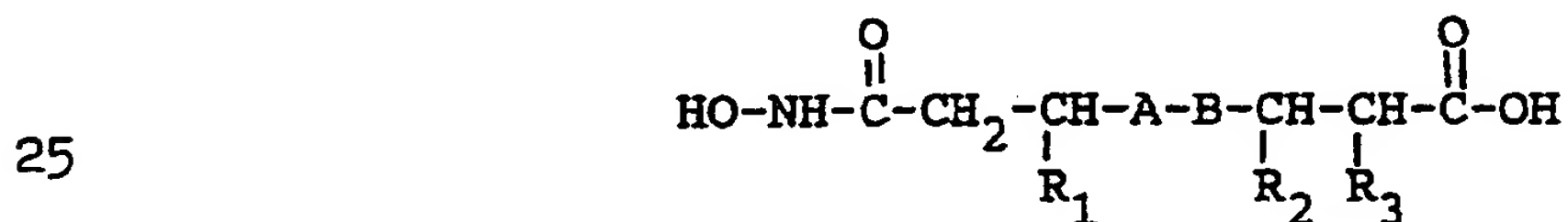
R_5 is hydrogen, C_1-C_6 methyl, C_1-C_6 alkoxy, C_1-C_6 alkyl, di(C_1-C_6 alkoxy)carbonyl, arylmethoxycarbonyl, (C_1-C_6 alkyl)aminocarbonyl or arylaminocarbonyl;

15 R_6 is hydrogen or methyl;

R_2 and R_4 may be taken together to form a $(CH_2)_n$ ring wherein n is 4 to 11; or R_4 and R_5 may be taken together to form a $(CH_2)_3$ ring.

The above compounds disclosed by Handa, et al. are alleged to inhibit collagenase.

20 In European Patent Application No. 0 262 053, Fournie-Zaluski, et al. disclose compounds of the formula:



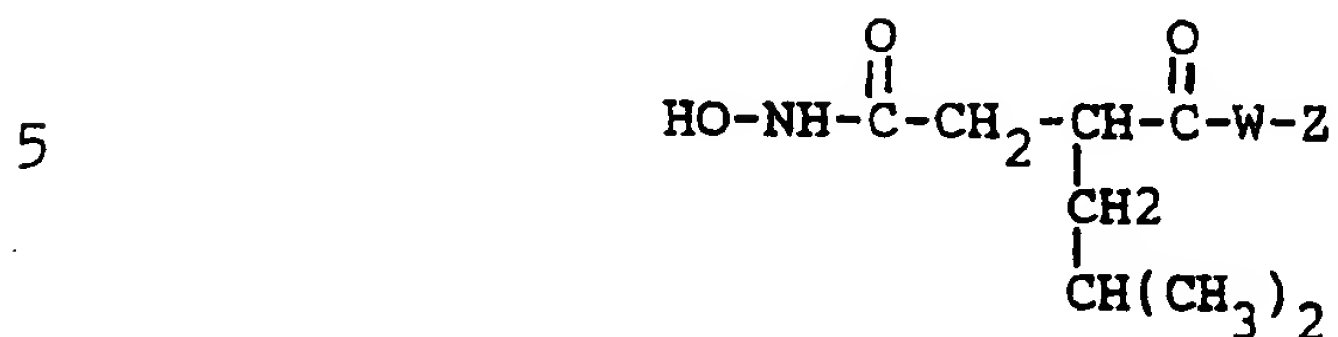
wherein R_1 is a saturated C_1-C_{10} alkyl;

R_2 and R_3 are the same or are different and represent hydrogen or a C_1-C_{10} saturated alkyl; and

30 A-B is either $-\overset{\text{O}}{\parallel}{\text{C}}-\text{NH}-$ or $-\text{NH}-\overset{\text{O}}{\parallel}{\text{C}}-$.

It is alleged that compounds of this formula inhibit collagenase.

1 Cartwright, et al. in European Patent
Application No. 274 453 discloses compounds of the
formula:

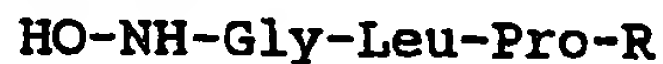


wherein W represents valine, lysine, norleucine or
methionine; and

10 Z represents an amino radical or an
alkylaminol in which the alkyl group contains 1 or 2
atoms of carbon and is substituted by a phenyl or a
trifluorophenyl.

It is alleged that these compounds inhibit
15 collagenase.

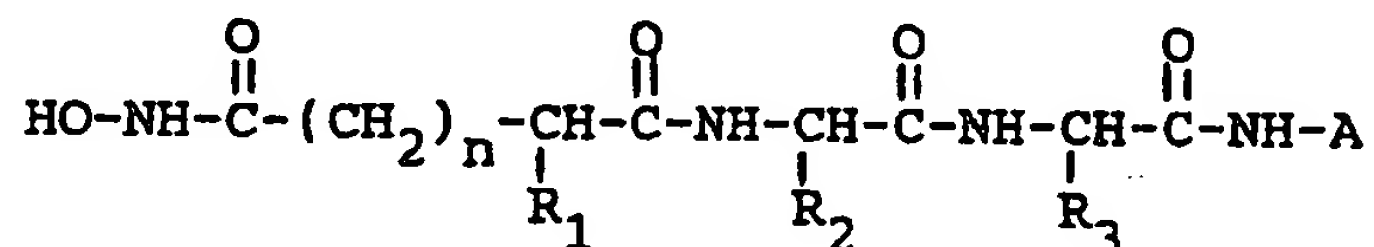
In U.S. Patent Nos. 4,687,841 and 4,720,486,
Spilburg, et al. disclose tripeptides of the formula:



20 wherein R represent hydrogen, agaroses or an α -amino
protecting group such as an alkanoyl, aroyl or
cycloalkanoyl.

These compounds allegedly function either as
collagen inhibitors or as affinity resins for the
purification of vertebrate collagenase.

25 Wolanin, et al. in U.S. Patent No. 4,771,038
disclose compounds having the formula:



30 wherein R_1 is C_2 - C_7 alkyl;

R_2 and R_3 may be the same or different and may
be an amino acid residue chosen from the following:

35

1 glycine, alanine, valine, leucine, isoleucine,
phenylalanine, tyrosine, tryptophan, serine, threonine,
cysteine, methionine, asparagine, glutamine, lysine,
arginine, glutamic acid and aspartic acid, such that
5 each amino residue, however, must not have an acidic
terminus, but optionally may have an acidic side chain;
n is either 1 or 2; and

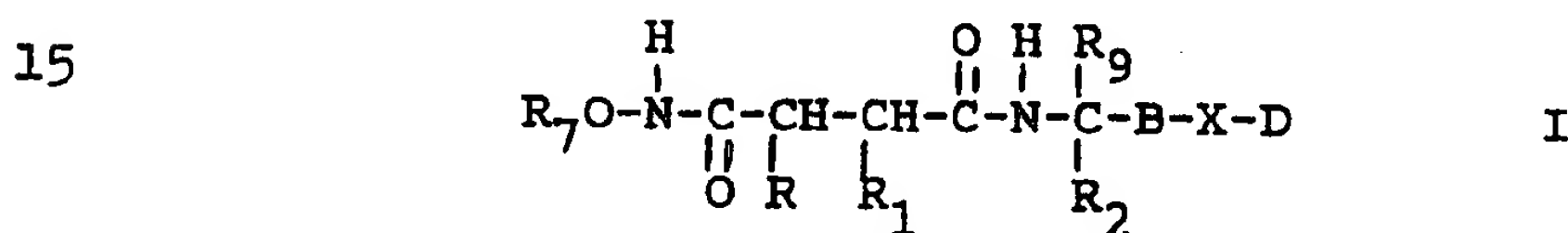
A is hydrogen or is $-\text{CHR}_4-\text{CO}-\text{NH}_2$, where R_4 is
an amino acid residue.

10 Compounds of this formula are alleged to
inhibit metalloproteases, particularly endopeptidases
such as collagenase.

In addition to patents, the scientific
literature also contains references to many collagenase
inhibiting compounds. Clark, et al. (Life Sciences 37:
15 575-578 (1985)) refer to N[[5-chloro-2-benzothiazolyl]
thiophenyl]acetyl]-L-cysteine, said to be a powerful
mammalian collagenase inhibitor. Deleaisse, et al.
(Biochem Biophys. Res. Comm. 133: 483-490, 1985) also
refer to an inhibitor N-[3-N-(benzyloxy-carbonyl)-amino-
20 1-(R)-carboxypropyl]-L-leucyl-O-methyl-L-tyrosine-N-
methylethylamide. Gray, et al. (Biochem. Biophys. Res. Comm.
101: 1251-1258, 1981) disclose a number of thiol-
containing analogues of the collagen cleavage site.
Additional thiol-containing peptides are disclosed by
25 Gray, et al. in J. Cell Biochem., 32: 71-77, 1986.
Carboxyalkyl peptide analogues are described in Gray, et
al. in Federation Proc. 44: 1431, 1985. Miller, et al.
and Gray, et al. also disclose thiol-containing peptides
in abstracts. [Fed. Proc. 45: 1859 (1986) and FASEB J.
30 2: A345 (1988), respectively]. Mookhtiar, et al. also
discloses phosphoramidate inhibitors of collagenase.
(see Biochemistry, 26, 1962 (1987)).

1 Despite the large number of compounds showing
 inhibitory properties, the therapeutically useful
 commercially available compounds are very few in number
 and are not altogether satisfactory in all respects for
 5 clinical use. Therefore, a continued need exists for an
 extremely potent and highly specific collagenase
 inhibitor which will have widespread therapeutic and
 commercial application. It has now been discovered that
 a small class of novel hydroxamic acid-containing
 10 tripeptides provides a level of collagenase inhibition
 not heretofore observed in the known inhibitory
 compounds.

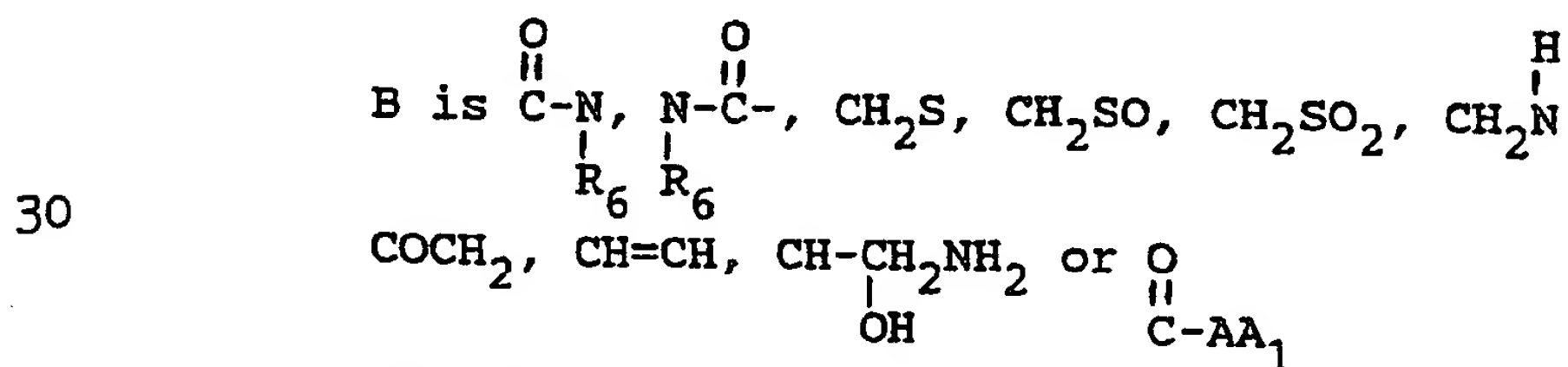
The present invention relates to compounds of
 the formula:



and pharmaceutically acceptable salts thereof wherein

R and R₁ are independently hydrogen, lower
 alkyl, aryl or aryl lower alkyl;

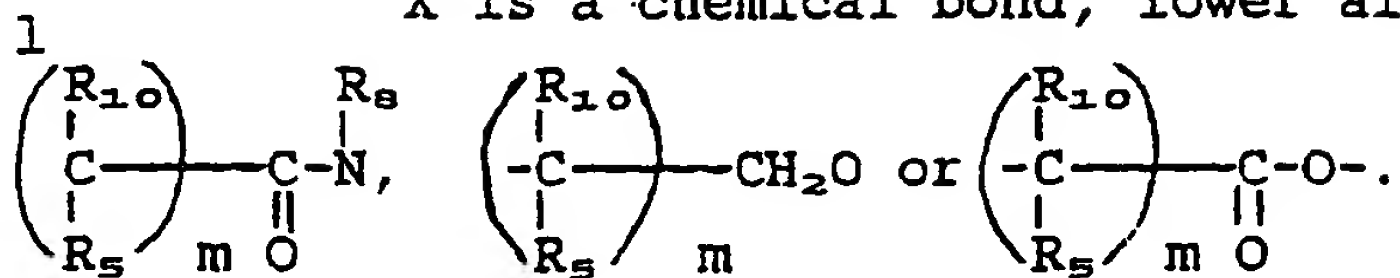
20 R₂ is aryl lower alkyl or heterocyclic lower
 alkyl; said R₂ being unsubstituted or mono- or di-
 substituted with chloro, fluoro, bromo, halo, nitro,
 carboxy, lower carbalkoxy, cyano, lower alkanoyl,
 25 trifluoromethyl, lower alkyl, hydroxy, lower alkoxy,
 formyl, amino, lower alkylamino, dilower alkylamino,
 mercapto, lower alkylthio or mercapto lower alkyl;



AA₁ is an amino acid residue;

35

X is a chemical bond, lower alkylene,



5 R_9 and R_{10} are independently hydrogen, methyl or ethyl,

D , R_5 , R_6 , R_7 , and R_8 are independently hydrogen or lower alkyl; and

m is 1, 2, or 3, with the proviso that when B

10 is $\begin{array}{c} O \\ || \\ C-N- \\ | \\ H \end{array}$ and X is a chemical bond or lower alkylene then

R_2 is not unsubstituted benzyl or benzyl monosubstituted with hydroxy, or lower alkoxy and with the further

15 proviso that when B is $\begin{array}{c} O \quad H \\ || \quad | \\ C-N \end{array}$ or $\begin{array}{c} O \\ || \\ C-AA_1 \end{array}$, and X is $\begin{array}{c} O \\ || \\ CH-C-N \\ | \quad | \\ R_5 \quad R_8 \end{array}$,

then R_2 is not unsubstituted indole or imidazole or unsubstituted benzyl or benzyl monosubstituted with hydroxy or lower alkoxy.

20 The present invention also relates to a pharmaceutical composition for the treatment of collagenase related disorders which comprises an effective amount of the aforementioned compounds and a pharmaceutical carrier therefor.

25 The present invention further relates to a method of treating a mammalian collagenase-related disorder which comprises administering to a mammal in need of treatment an inhibitory effective amount of the compound of Formula I.

30 As defined herein, the term "lower alkyl," when used alone or in combination with other groups, represents an alkyl group containing one to six carbon

35

1 atoms. These groups may be straight chain or branched.
They include such groups as methyl, ethyl, propyl,
isopropyl, butyl, isobutyl, sec-butyl, t-butyl, amyl,
pentyl, hexyl and the like. It is preferred that the
5 alkyl group contains 1-4 carbon atoms.

The term "aryl," when used alone or in
combination with other groups, represents an aromatic
moiety containing six to ten ring carbon atoms. This
group includes phenyl, α -naphthyl, and β -naphthyl, and
the like.

10 The term "aryl lower alkyl" refers to a group
which contains a lower alkylene substituent to which is
bonded an aryl group. Examples include benzyl, α -
naphthylenemethyl, β -naphthylenemethyl, phenethyl, α -
and β -naphthyleneethyl and the like. The preferred
15 arylalkyl groups are benzyl and α - and β -naphthylene-
methyl. The especially preferred aryl lower alkyl is α -
and β -naphthylene methyl.

The term "heterocyclic," when used alone or in
combination, refers to a cyclic group containing at
20 least one ring hetero atom selected from sulfur, oxygen
or nitrogen. The heterocyclic substituent contemplated
by the present invention includes heteroaromatics and
saturated and partially saturated heterocyclics. These
heterocyclic may be monocyclic, bicyclic or polycyclic
25 and form fused rings. They may contain up to 18 ring
atoms, up to 4 ring heteroatoms and up to a total of 17
ring carbon atoms and up to a total of 25 carbon atoms.
The heterocyclics are also intended to include the
benzoheterocyclics. Representative heterocyclics
30 include thienyl, benzothienyl, naphthothienyl, furyl,
pyranyl, pyrazolyl, pyrrolyl, imidazolyl, isoindolyl,
indazolyl, isooxazolyl, indolyl, thiazolyl, piperazinyl,

35

1 quinolyl, triazolyl, tetrazolyl, isoquinolyl,
benzofuryl, benzothienyl, morpholinyl, benzoxazolyl,
tetrahydrofuryl, pyranyl, indazolyl, purinyl, indolinyl,
pyrazolindinyl, imidazolinyl, imadazaolidinyl,
5 pyrrolidinyl, furazanyl, N-methylindolyl, furfuryl,
pyridyl, tetrahydrofuryl, pyridazinyl, pyrimidinyl,
pyrazinyl, epoxy, aziridino, oxetanyl, azetidiny, and
the like. It is preferred that the heterocyclic moiety
contain up to 10 ring atoms and up to a total of 4 ring
10 heteroatoms. It is also preferred that the heterocyclic
moiety be benzoheterocyclic. Further it is preferred
that the heterocyclic moiety contain at least 1 ring
nitrogen atom, and it is most preferred that the only
ring heteroatom is nitrogen. It is also most preferred
15 that the heterocyclic ring is an heteroaromatic in which
the only heteroatom on the ring is nitrogen. It is
especially preferred that the heterocyclic group
contains only 1 ring nitrogen atom and be
heteroaromatic. Examples of the preferred heterocycles
20 include pyrrolyl, imidazolyl, pyrazolyl, tetrazolyl,
pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl,
indoliziny, isoindolyl, indolyl, indazolyl, purinyl,
quinoliziny, quinolyl, and isoquinolyl, and the like.
The most preferred heterocyclic moiety is pyrrolyl,
pyridyl, indolyl, isoquinolyl and quinolyl. The
25 especially preferred heterocyclic ring is pyridyl,
especially 2, 3- or 4-pyridyl, and indolyl, especially
3-indolyl.

The term heterocyclic lower alkyl refers to a
group which contains a lower alkyl substituent to which
30 is bonded a heterocyclic group. Examples include
pyridylmethyl, indolylmethyl, pyridylethyl,
indolyethyl, quinolylmethyl, and the like.

1 The term "alkanoyl" includes lower alkyl
ketones and aldehydes. Examples include formyl, acetyl,
propanoyl, butanoyl, and the like.

5 The term AA₁ refers to the naturally occurring
amino acids. Preferably, these amino acids are α -amino
acids. Most preferably, they are the twenty naturally
occurring amino acids. These amino acids are recited
below with the abbreviation for each used hereinafter in
the specification and claims:

10

Ala - Alanine Thr - Threonine

Gly - Glycine Cys - Cysteine

15

His - HistidineMet - Methionine

Leu - Leucine Pro - Proline

Ile - IsoleucineLys - Lysine

20

Ser - Serine Arg - Arginine

Asp - Aspartic AcidAsn - Asparagine

25

Glu - Glutamic AcidGln - Glutamine

Phe - PhenylalanineTyr - Tyrosine

Trp - TryptophanVal - Valine

30

These are the most preferred amino acids.
Other amino acids contemplated by the present invention
include naphthylalanine (Nal), hydroxylysine (Hyl),

35

1 hydroxyproline (Hyp), ethylglycine (EtGly), amino adipic
acid (Aad), 2-aminobutyric acid (Abu), norvaline (Nva),
norleucine (Nle), ornithene (Orn), sarcosine (Sar), N-
methylglycine (MeGly), N-methylisoleucine (MeIle), N-
5 methylvaline (MeVal) and dopamine (DOPA).

The most preferred AA1 is glycine, alanine,
valine, leucine, isoleucine, proline and N-methyl
alanine. The especially preferred amino acid is
alanine.

10 The alkyl groups, aralkyl groups, aryl groups,
the heterocyclic groups and the heterocyclic alkyl
groups as defined herein may be unsubstituted or
substituted with electron donating or electron
withdrawing groups. The terms "electron withdrawing"
and "electron donating" refer to the ability of a
15 substituent to withdraw or donate electrons relative to
that of hydrogen if the hydrogen atom occupied the same
position in the molecule. These terms are well
understood by one skilled in the art and are discussed
in Advanced Organic Chemistry, by J. March, John Wiley
20 and Sons, New York, N.Y. pp. 16-18 (1985), and the
discussion therein is incorporated herein by reference.
Electron withdrawing groups include halo, including
bromo, fluoro, chloro and iodo; nitro; carboxy; lower
carbalkoxy; cyano; lower alkanoyl; mono, di-, tri-halo
25 (lower) alkyl, e.g., trifluoromethyl; carboxyamido;
formyl; sulfonyl; sulfinyl; ammonium; mono-, di-, tri-
and tetra lower alkylammonium; heterocyclic; aryl, and
the like. Electron donating groups include such groups
as hydroxy; lower alkoxy; lower alkyl; amino; lower
30 alkyl amino; di-(lower alkyl amino); aryloxy; mercapto;
lower alkylthio; mercapto lower alkyl; lower alkyldithio
and the like. The preferred substituents are lower

35

1 alkyl, chloro, bromo, fluoro, lower alkoxy, lower
alkylamino, diloweralkylamino, nitro, sulfonyl,
mercapto, lower alkylthio, lower alkanoyl, and
trifluoromethyl.

5 The preferred values of R_7 are hydrogen and
alkyl containing 1-4 carbon atoms. The especially
preferred R_7 is methyl and hydrogen. The most preferred
is hydrogen.

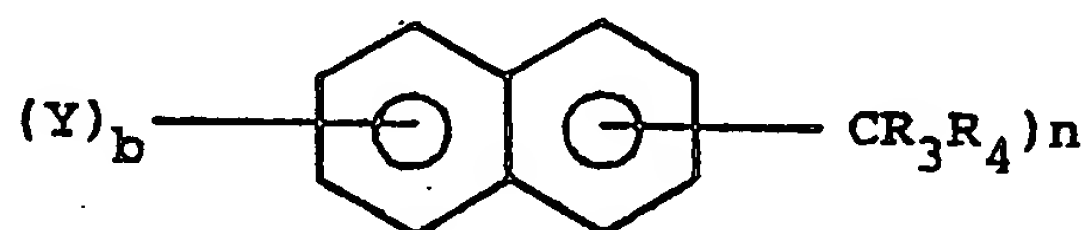
It is preferred that R is hydrogen or methyl.
10 The preferred value of R_1 is a butyl group, i.e.,
isobutyl, n-butyl, t-butyl or sec-butyl. The most
preferred value of R_1 are sec-butyl and especailly t-
butyl.

As indicated hereinabove, R_2 may be arylalkyl
15 or heterocyclicalkyl.

A preferred arylalkyl is dopa or 3,-4-
dimethoxybenzyl.

Another preferred aryl alkyl is a
naphthylalkylene moiety of the formula:

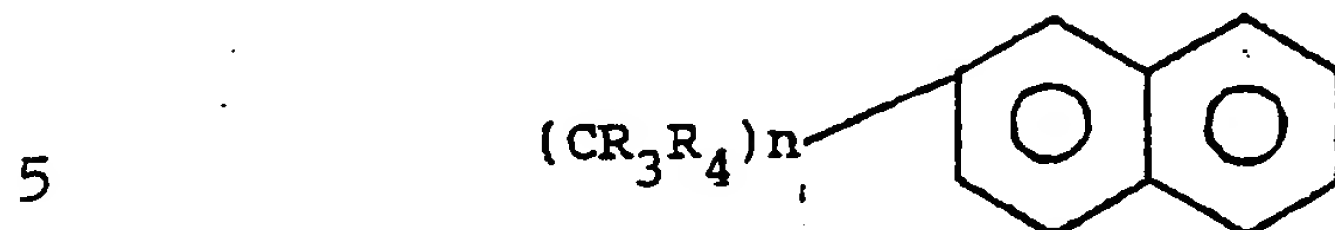
20



25 wherein R_3 , and R_4 are hydrogen or lower alkyl and n is
1 or 2, Y is hydrogen, halo, nitro, carboxy, lower
carbalkoxy, cyano, lower alkanoyl, trifluoromethyl,
lower alkyl, hydroxy, lower alkoxy, formyl, amino, lower
alkyl amino, dilower alkyl amino, mercapto, lower alkyl
thio or mercapto lower alkyl, and b is 1 or 2. The
30 preferred Y is H or CH_3 . It is preferred that b is 1.
The most preferred R_3 and R_4 are hydrogen. Moreover it
is preferred that n is 1.

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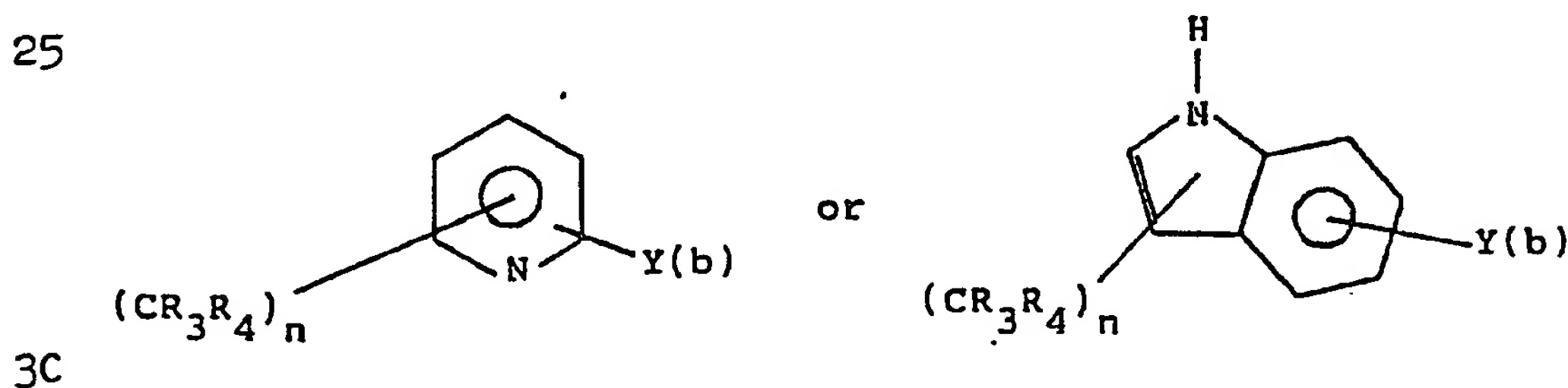
1 The most preferred naphthylalkylene moiety is a
2-naphthylalkylene moiety of the formula:



wherein R_3 , R_4 and n are as defined hereinabove.
Moreover, the most preferred value of naphthylalkylene
10 for R_2 is 2-naphthylmethylene.

As defined herein, R_2 can also be a
heterocyclic lower alkyl moiety, i.e., $(\text{CR}_3\text{R}_4)_n$ -
heterocyclic, wherein, R_3 , R_4 , n and heterocyclic are as
defined hereinabove. The preferred heterocyclic groups
15 are described hereinabove. It is preferred that the
heterocyclic group contains a nitrogen ring atom.
Furthermore, the preferred heterocyclic groups are
heteroaromatic. Finally, the most preferred
heterocyclic groups are heteroaromatic and contain a
nitrogen ring atom. Examples of the most preferred
20 heterocyclic are pyrrolyl, pyridyl, indolyl,
isoquinolyl, quinolyl and the like.

Especially preferred R_2 have the formula:



35

1 wherein R_3 , R_4 , Y, b and n are as defined hereinabove.
 The substituent $(CR_3R_4)_n$ can be substituted on the
 carbon ring atoms in the heteroaryl or can replace the
 hydrogen on the NH ring atom. It is preferred that the
 5 $(CR_3R_4)_n$ groups be substituted on the 2-, 3-, or 4-
 position of the pyridyl and the 2-, or especially the 3-
 position of the indolyl. It is preferred that n is 1
 and it is also preferred that R_3 and R_4 are hydrogen.

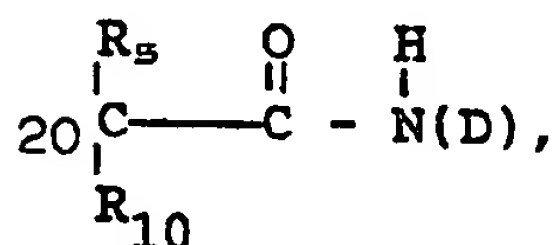
It is preferred that Y is hydrogen, lower
 10 alkyl or lower alkoxy. Furthermore, it is preferred
 that b is 1.

The preferred value of m is 1.

The preferred value of R_9 is methyl and
 especially hydrogen. Similarly, the preferred value of
 15 R_{10} is methyl, and especially hydrogen.

The preferred value of D is methyl, ethyl and
 especially hydrogen.

Further, the preferred value of X-D is

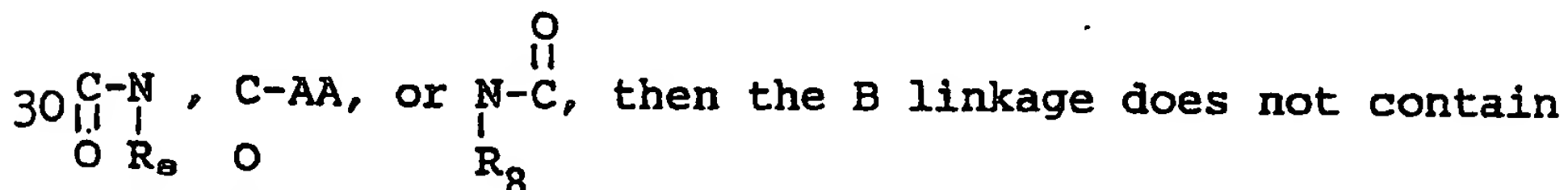


wherein R_{10} is methyl or hydrogen and D is methyl, ethyl

or hydrogen. The preferred X - D is $CH_2 \overset{O}{\parallel} C - NH_2$

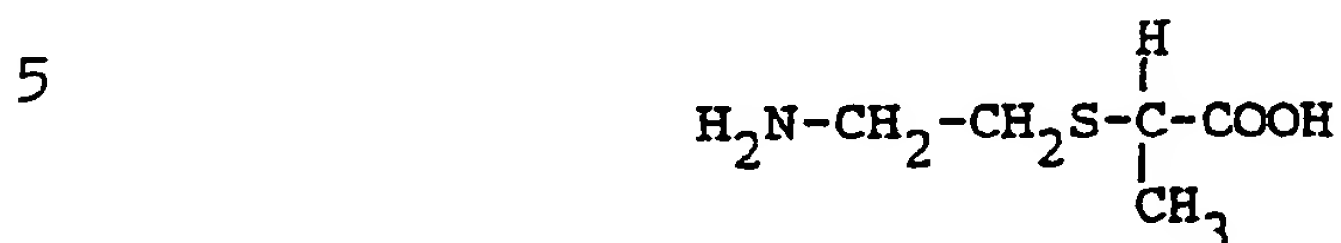
25 All combinations and permutations on the
 various variables described hereinabove are contemplated
 by the present invention.

It is to be noted that when B is other than



an amide linkage. Under these circumstances, B is a
 pseudopeptide (4). If a peptide is written as AA_2 4

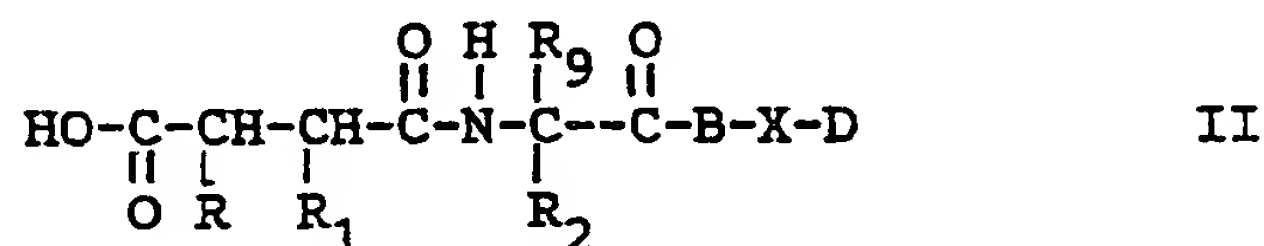
1 [B]AA₃ where AA₂ and AA₃ are amino acids, this means
 that the amide linkage between AA₂ and AA₃ is replaced
 by B. For example, Gly (CH₂S)Ala, means that alanine
 and glycine are linked by a CH₂S group.



Gly Ala

10 The compounds of the present invention are
 prepared by art recognized procedures. The starting
 materials of the reagents employed in the reactions
 hereinbelow maybe commercially available or may be
 prepared in accordance with standard techniques. A
 thorough discussion of the method of preparation is
 15 found in U.S. Patent No. 4,599,361, the teachings of
 which are incorporated herein by reference.

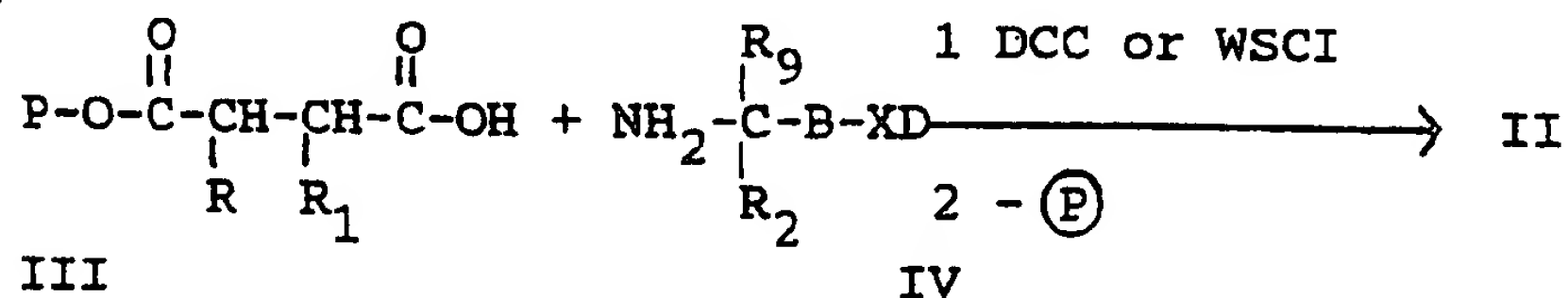
 More specifically, the compounds of the
 present invention can be prepared by reacting an
 acylating derivative of the hydroxamic acid (e.g., acid
 20 lower alkyl ester and the like) of Formula II



25 wherein R, R₁, R₂, R₉, AA₁, B, D and X are as defined
 hereinabove, with O-benzylhydroxylamine followed by
 hydrogenation. Alternatively, the hydroxamic acid can
 be prepared by coupling the acid directly with
 hydroxylamine using a coupling agent such as ethyl
 30 chloroformate. If desired, the products of Formula I
 may be separated into the individual isomers by
 chromatography.

35

1 The dipeptide of Formula II may be prepared by
 any of the wide range of known methods. For example, a
 protected carboxylic acid derivative, of Formula III can
 be reacted with a peptide of Formula IV under amide
 5 forming conditions, as shown below.



10 wherein R, R₁, R₂, B and X are as defined hereinabove,
 and P is a carboxylic acid protecting group, such as
 lower alkyl, e.g., t-butyl, which can easily be removed
 after the coupling shown hereinabove takes place. Among
 the more commonly used techniques are coupling using N,
 15 N'-dicyclohexylcarbodiimide (DCC) or water soluble
 carbonyl diimide (WSCl) or the solid phase Merrifield
 synthesis, in which a protected amino acid is bound to a
 resin particle as an ester bond. Amino acids having
 functional groups such as tyrosine are generally
 20 protected with an easily removed blocking group, which
 are well known to the skilled artisan. Each of these
 techniques is equally suitable for the present purposes.

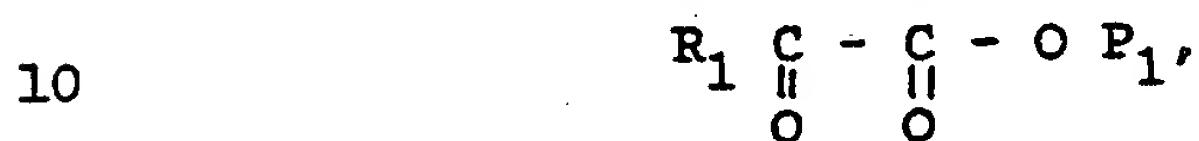
The compounds so produced may be purified by
 chromatography, electrophoresis, or any other suitable
 25 means.

The corresponding protected carboxylic acid of
 Formula III, in which R is hydrogen, such as
 monosubstituted succinic acid lower alkyl ester, can be
 prepared by reacting diethyl succinate and an aldehyde
 of the formula R₁₁CHO in the presence of a strong base,
 30 such as alkali t-butoxide, wherein R₁₁ is a homolog of
 R₁ containing one less carbon atom (i.e. R₁ is R₁₁-CH₂).
 The product thereof is hydrogenated. The resulting

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1 monoester is esterified, such as by reacting isobutylene
 in the presence of an acid (H^+) and the product thereof
 is hydrolyzed in the presence of a base, e.g. NaOH.
 This procedure is described in U.S. Patent No.
 4,771,038, the discussion of which is incorporated
 5 herein by reference.

Alternatively when R is alkyl, hydrogen, aryl
 or aryl, lower alkyl, the compound of III is prepared by
 reacting a protected oxalic acid of Formula V.



wherein P_1 is a protecting group such as benzyl with a
 phosphorous ylide-type compound, such as triethyl-
 phosphorous propionate, in the presence of a strong base
 (e.g., sodium hydride) under Wittig-Horner reaction
 15 conditions. An ylide-type compound can be prepared from
 a trialkoxy phosphorous such as $(EtO)_3P$ and an -bromo
 carboxylic acid ester, e.g., $R-CH-COOEt$, under Arbuzov
 Br

20 reaction conditions.

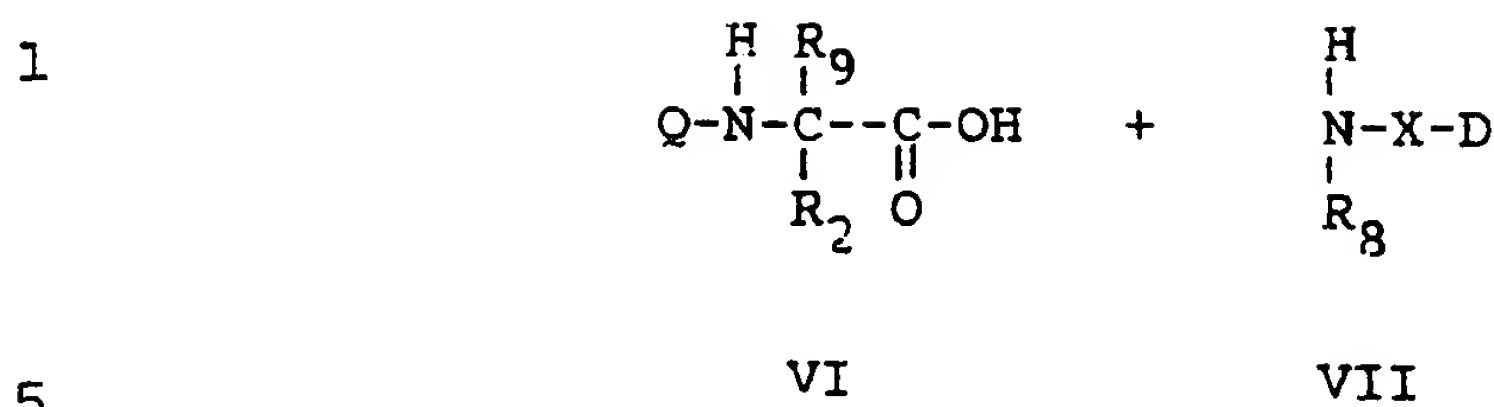
The product is then hydrogenated to form the
 compound of Formula III.

The compound of Formula IV can also be
 prepared by art recognized techniques. For example,
 when B is $\begin{array}{c} \text{C}-\text{N} \\ \parallel \quad | \\ \text{O} \quad R_8 \end{array}$ or $\begin{array}{c} \text{C}-\text{AA}_1 \\ \parallel \\ \text{O} \end{array}$, in which R_8 and AA_1 are as
 25

defined hereinabove, the compound of Formula IV can be
 prepared by reacting a protected amino acid acylating
 derivative of Formula VI with an amine of Formula VII as
 follows:

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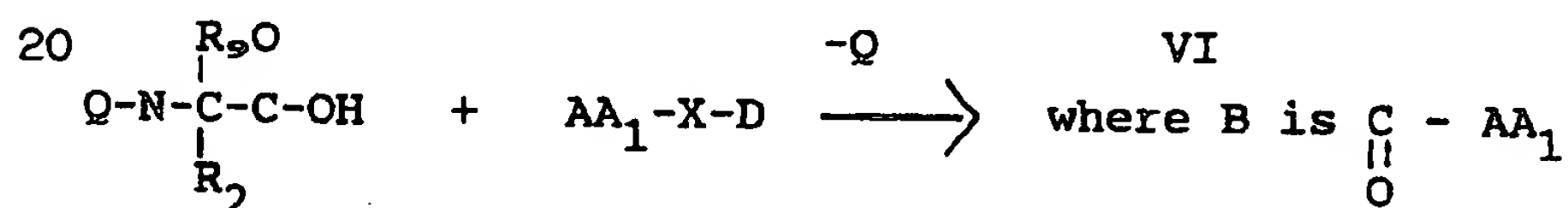
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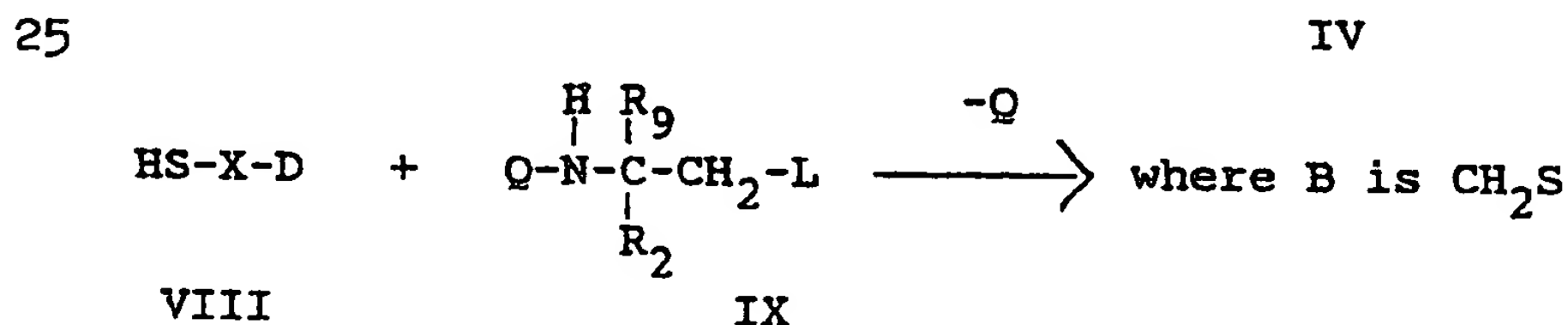
removal of
protecting IV where B is $\begin{array}{c} \text{C} - \text{N} \\ || \quad | \\ \text{O} \quad \text{R}_6 \end{array}$
groups $\xrightarrow{\hspace{1cm}}$

10 under amide forming conditions. In this scheme, Q is an amino protection group, such as t-boc, and B is $\begin{array}{c} \text{C}-\text{N} \\ || \quad | \\ \text{O} \quad \text{R}_6 \end{array}$,
and X and D₁, R₂ and R₆ are as defined hereinabove. If D contains a carboxy group or a carboxy derivative which
15 is also reactive under these reaction conditions, then these groups should be protected before the coupling takes place.

When B is $\begin{array}{c} \text{C}-\text{AA} \\ || \\ \text{O} \end{array}$, the reaction is very similar



In the case when B is CH₂S, an exemplary procedure for making the product of IV is as follows:



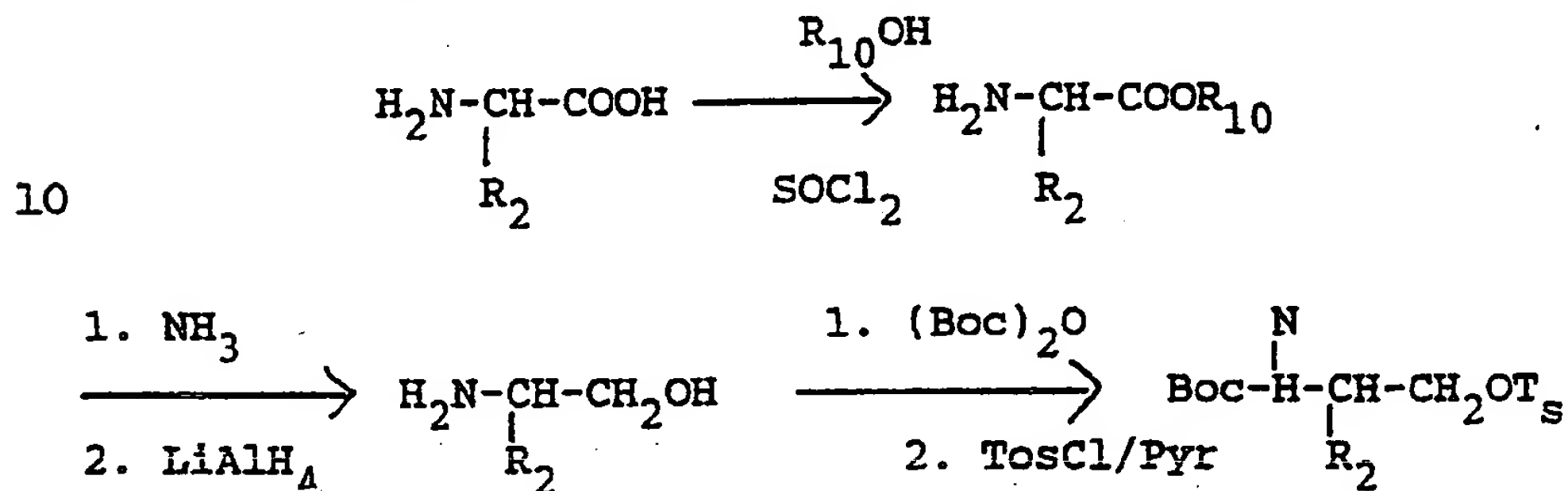
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In this scheme, R₂, X, Q and D are as defined hereinabove and L is a good leaving group such as tosylate, halide and the like. In this reaction, the

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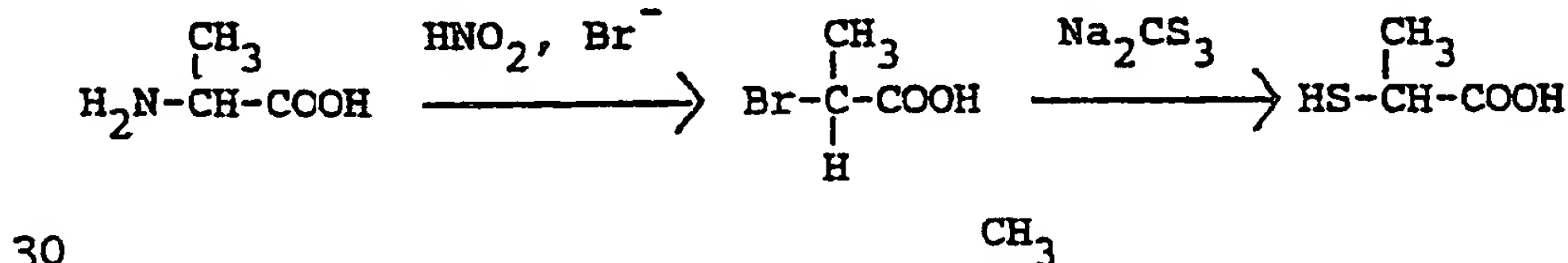
1 thiol of Formula VIII is reacted with a protected amino
 group having a good leaving group under nucleophilic
 substitution reaction conditions. Removal of the
 protecting group generates the product IV, wherein B is
 5 CH_2S .

The compound of Formula IX can be generated by
 the following exemplary reaction scheme:



In this scheme B is CH_2S , R_{10} is lower alkyl,
 Boc is butyloxycarbonyl, Q is an amino protecting group
 and OT_S is tosylate, and L is a good leaving group. The
 amino acid of Formula X is esterified under
 esterification conditions and the resulting ester is
 20 reduced with a reducing agent, such as LiAlH_4 . After
 protecting the amino group, a tosyl halide is reacted
 with the alcohol in base, such as pyridine to form the
 corresponding tosylate.

An exemplary scheme for forming the compound
 25 of Formula VIII is as follows:



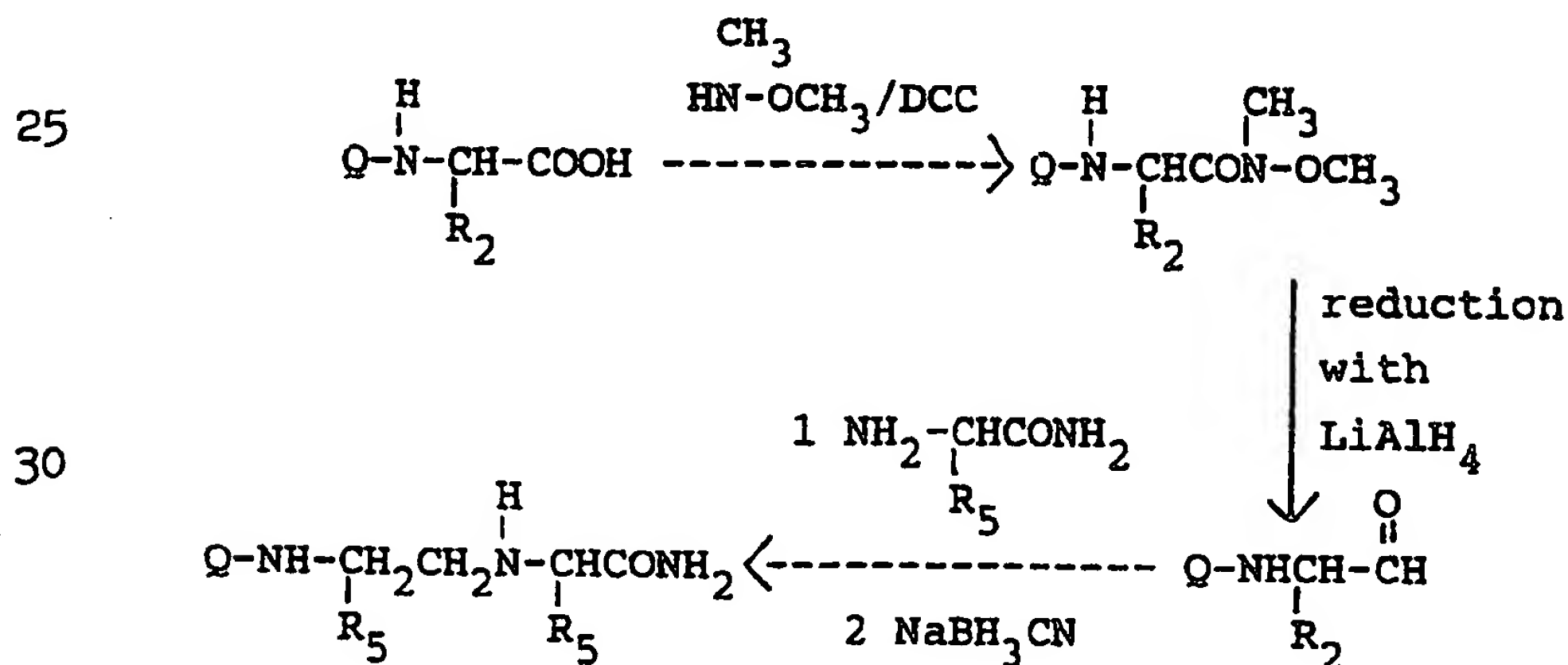
In this example, X-D is $\text{CH}-\text{COOH}$. The compound
 of Formula X is halogenated by, for example, reacting it
 with nitric acid and a bromide salt (e.g. NaBr), with

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1 retention of configuration. Under mercapto forming
 conditions, the halide is reacted with a salt of a
 mercapto, such as $\text{CS}_3=$, to form the corresponding thiol,
 with inversion of configuration.

5 The sulfoxides, i.e., compounds when B is
 CH_2SO and the sulfones, i.e., compounds wherein B is
 CH_2SO_2 can be prepared from the corresponding
 thiols. Thus, for example, 1 mole of the compounds of
 Formula IV, wherein B is CH_2S or SCH_2 can be reacted
 10 with one mole of oxidizing agents, such as 30% H_2O_2 ,
 NaIO_4 , t-BuO-Cl, acyl nitrite, sodium perborates,
 peracids and the like to form the corresponding
 sulfoxides. The sulfoxides in turn can be further
 oxidized to the corresponding sulfones by reacting the
 sulfoxide with another mole of oxidizing agent, such as
 15 H_2O_2 , KMnO_4 , sodium perborate, potassium hydrogen
 persulfate, and the like, to form the compound of
 Formula IV wherein B is CH_2SO_2 or SO_2CH_2 . If excess
 oxidizing agents were present, then the sulfide can be
 directly converted to the sulfone without isolation of
 20 the sulfoxides.

When B is CH_2NH , an exemplary procedure for
 making the product of IV is as follows



35

1 wherein Q, R₂, R₅ are as defined hereinabove. In the
exemplary scheme, R₉ is hydrogen.

A protected amino acid is reacted with N, O-
dimethylhydroxylamine in the presence of DCC or WSCI
under amide forming conditions to form the corresponding
5 hydroxamate. Reduction of the hydroxamate with a
reducing agent such as LiAlH₄ forms the corresponding
aldehyde. The aldehyde is reacted with an amino acid
derivative, such as an amide to form the Schiff base
which is then reduced with a reducing agent, NaBH₃CN,
10 under Castro NaBH₃CN reducing conditions to form the
corresponding compound of Formula IV wherein B is CH₂NH.

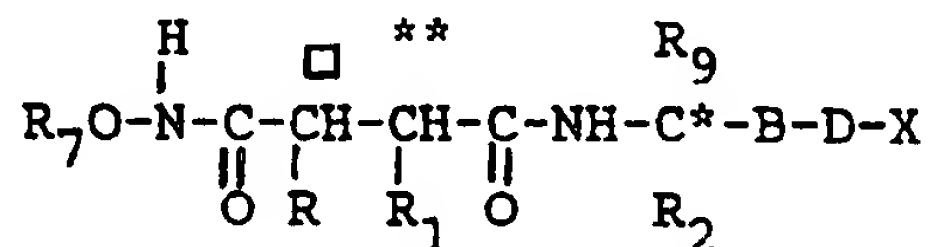
The ketomethylene compounds of the present

15 invention ($\text{CH}_2\overset{\text{O}}{\parallel}\text{C}$) can be prepared by techniques known to
one skilled in the art. These techniques are described
by Jennings-White, et al. in Tetrahedron Letters, 73,
2533-2534 (1982), Almquist, et al. in J. Med. Chem., 23,
1392-1398 (1980), Almquist, et al. in J. Med. Chem.,
25, 1292-1299 (1982) and Holladay, et al. in
20 Tetrahedron Letters, 24, 4401-4404 (1983). These papers
describe various methods for preparing ketomethylene
linkages, and the procedures therein for can be used to
make the ketomethylene linkages in compounds of the
present invention. These references are therefore
25 incorporated herein by reference as if they were set
forth fully hereinbelow.

If the substituents on the starting compounds
or intermediates themselves are reactive, then the
substituents can themselves be protected according to
30 techniques known to one skilled in the art. A variety
of protecting groups known in the art may be employed.
Examples of many of these possible groups may be found

1 in "Protective Groups in Organic Synthesis" by W. Green,
John Wiley and Son, 1981.

The compounds of the invention contain at
least one asymmetric carbon atom, which is designated in
5 the formula below by an asterisk



Furthermore, the groups CH(R) and CH(R1) and

10 $\begin{array}{c} \text{R}_{10} \\ | \\ \text{C} \\ | \\ \text{R}_5 \end{array}$ are pseudoasymmetric groups, [(**) and (\square)] each of
which can contain additional asymmetric carbon when R or
R₁ is other than hydrogen and R₁₀ is other than R₅.
Each of the asymmetric carbons gives rise to chiral
15 centers, and each of the chiral centers can exist in
either the R or S forms. Each of the various
stereoisomers, including the enantiomers and
diastereoisomers, are contemplated by the present
invention. The pure stereoisomers as well as a mixture
20 thereof are contemplated by the present invention.
However, it is preferred that the configuration at the
asterisked carbon be S. It is also preferred that the
configuration around the double asterisked carbons also
be in the S form. In the more preferred form, the
25 configuration around each of the indicated chiral
centers is in the S form.

Moreover, these stereoisomers can be separated
by art recognized techniques known in the art. For
example, the amino acids which are commercially
30 available and are substantially optically pure, are used
as starting materials onto which the peptide builds.
Therefore, the various stereoisomeric products formed by

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1 the reaction described hereinabove would be
diastereomeric pairs, which can be resolved by standard
chromatographic techniques.

The present new compound form salts with acids
when a basic amino function is present and salts with
5 bases when an acid function, i.e., carboxy, is present.
All such salts may be useful in the isolation and/or
purification of the new products. Of particular value
are the pharmaceutically acceptable salts with both
10 acids and bases. Suitable acids include, for example,
hydrochloric, sulfuric, nitric, benzenesulfuric,
toluenesulfonic, acetic, malic, tartaric and the like
which are pharmaceutically acceptable. Basic salts for
pharmaceutical use are the Na, K, Ca and Mg salts.

15 In those peptides in which Arg is added, acid
addition salts may also be prepared, particularly
acetate or hydrochloride salts. Although for obvious
reasons, pharmaceutically acceptable salts are
preferred, the invention is not limited to them since
20 non-pharmaceutically acceptable salts may prove useful
in isolating the compounds of the invention.

The compounds of the present invention can be
administered to the host in a variety of forms adapted
to the chosen route of administration, i.e., orally,
intravenously, intramuscularly or subcutaneous,
25 topically or inhalation routes. Topical application is
extremely important when treating dermatological
diseases.

The compounds of the present invention can be
employed in the treatment of any disease in which
30 collagenase has been implicated as a central factor;
such as for example, corneal ulceration, osteoporosis,
periodontitis, Paget's disease, gingivitis, tumor

1 invasion, dystrophic epidermolysis bullosa, systemic
ulceration, epidermal ulceration, gastric ulceration,
and the like.

The pharmaceutical compositions according to
5 the invention may, for example, take the form of
ointments, gels, pastes, creams, sprays (including
aerosols), lotions, suspensions, solutions and emulsions
of the active ingredient in aqueous or non-aqueous
dilutents, syrups, granulates or powders.

10 The pharmaceutical compositions which are
ointments, pastes, creams and gels can, for example,
contain the usual diluents, e.g. animal and vegetable
fats, waxes, paraffins, starch, tragacanth, cellulose
derivatives, polyethylene glycols, silicones,
15 bentonites, silic acid, talc and zinc oxide or mixtures
of those substances.

The pharmaceutical compositions which are
powders and sprays, can, for example, contain the usual
diluents, e.g. lactose, talc, silic acid, aluminum
hydroxide, calcium silicate, and polyamide powder or
20 mixtures of these substances. Aerosol sprays can, for
example, contain the usual propellants, e.g.
chlorofluorohydrocarbons.

The active compound may be orally
administered, for example, with an inert diluent or with
25 an assimilable edible carrier, or it may be enclosed in
hard or soft shell gelatin capsule, or it may be
compressed into tablets, or it may be incorporated
directly with the food of the diet. For oral
therapeutic administration, the active compound may be
30 incorporated with excipients and used in the form of
ingestible tablets, buccal tablets, troches, capsules,
elixirs, suspensions, syrups, wafers, and the like.

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1 Such compositions and preparations should contain at
least 0.1% of active compound. For parental
administration they may be used in the form of a sterile
solution containing other solutes, for example, enough
5 saline or glucose to make the solution isotonic.

5 The physician will determine the dosage of the
present therapeutic agents which will be most suitable
and it will vary with the form of administration and the
particular compound chosen, and furthermore, it will
10 vary with the particular patient under treatment. He
will generally wish to initiate treatment with small
dosages, substantially less than the optimum dose of the
compound and increase the dosage by small increments
until the optimum effect under the circumstances is
15 reached. It will generally be found that when the
composition is administered orally, larger quantities of
the active agent will be required to produce the same
effect as a smaller quantity given parenterally. The
compounds are useful in the same manner as comparable
20 therapeutic agents and the dosage level is of the same
order of magnitude as is generally employed with those
other therapeutic agents.

When given orally, the therapeutic doses of
the compounds of the present invention are generally
effective, even in the nanomolar range, and these
25 compounds are effective in micromolar quantities in the
range of from about 10 to about 500 mg/kg of body weight
of treated mammal. When given parenterally, the
compounds are administered generally in dosages of, for
example, 0.01 mg/kg to about 200 mg/kg, also depending
30 upon the host and effect desired. The preferred dosage
ranges from 0.5 to 10 mg/kg of body weight of treated
mammal.

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1 The tablets, troches, pills, capsules and the
like may also contain the following: A binder such as
gum tragacanth, acacia, corn starch or gelatin;
excipients such as dicalcium phosphate; a disintegrating
5 agent such as corn starch, potato starch, alginic acid
and the like, a lubricant such as magnesium stearate;
and a sweetening agent such as sucrose, lactose or
saccharin may be added or a flavoring agent such as
peppermint, oil of wintergreen, or cherry flavoring.
10 When the dosage unit form is a capsule, it may contain,
in addition to materials of the above type, a liquid
carrier. Various other materials may be present as
coatings or to otherwise modify the physical form of the
dosage unit. For instance, tablets, pills, or capsules
15 may be coated with shellac, sugar or both. A syrup or
elixir may contain the active compound, sucrose as a
sweetening agent, methyl and propylparabens as
preservatives, a dye and flavoring such as cherry or
orange flavor. Of course, any material used in
20 preparing any dosage unit form should be
pharmaceutically pure and substantially non-toxic in the
amounts employed. In addition, the active compound may
be incorporated into sustained-release preparations and
formulations.

25 The active compound may also be administered
parenterally or intraperitoneally. Solutions of the
active compounds as a free base or pharmacologically
acceptable salt can be prepared in water suitably mixed
with a surfactant such as hydroxypropylcellulose.
30 Dispersions can also be prepared in glycerol, liquid
polyethylene glycols, and mixtures thereof and in oils.
Under ordinary conditions of storage and use, these

1 preparations contain a preservative to prevent the
growth of microorganisms.

The pharmaceutical forms suitable for
injectable use include sterile aqueous solutions or
dispersions and sterile powders for the extemporaneous
5 preparation of sterile injectable solutions or
dispersions. In all cases the form must be sterile and
must be fluid to the extent that easy syringability
exists. It must be stable under the conditions of
manufacture and storage and must be preserved against
10 the contaminating action of microorganisms such as
bacteria and fungi. The carrier can be a solvent or
dispersion medium containing, for example, water,
ethanol, polyol (for example, glycerol, propylene
glycol, and liquid polyethylene glycol, and the like),
15 suitable mixtures thereof, and vegetable oils. The
proper fluidity can be maintained, for example, by the
use of a coating such as lecithin, by the maintenance of
the required particle size in the case of dispersion and
by the use of surfactants. The prevention of the action
20 of microorganisms can be brought about by various
antibacterial and antifungal agents, for example,
parabens, chlorobutanol, phenol, sorbic acid,
thimerosal, and the like. In many cases, it will be
preferable to include isotonic agents, for example,
25 sugars or sodium chloride. Prolonged absorption of the
injectable compositions can be brought about by the use
in the compositions of agents delaying absorption, for
example, aluminum monostearate and gelatin.

Sterile injectable solutions are prepared by
30 incorporating the active compound in the required amount
in the appropriate solvent with various of the other
ingredients enumerated above, as required, followed by

1 filtered sterilization. Generally, dispersions are
prepared by incorporating the various sterilized active
ingredient into a sterile vehicle which contains the
basic dispersion medium and the required other
5 ingredients from those enumerated above. In the case of
sterile powders for the preparation of sterile
injectable solutions, the preferred methods of
preparation are vacuum drying and the freeze-drying
technique which yield a powder of the active ingredient
10 plus any additional desired ingredient from previously
sterile-filtered solution thereof.

The following examples are given to illustrate
the present invention. These examples are provided
solely for the illustration purposes. Therefore, the
15 invention should not be limited thereto.

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EXAMPLE 1

PREPARATION OF HYDROXAMIC ACID BASED COLLAGENASE

INHIBITORS: SYNTHESIS OF

5 A. 3-Ethoxycarbonyl-3-(2-methylpropyl)propanoic acid

Potassium t-butoxide, 24.7 g (0.35 M), was dissolved in 200 ml of refluxing t-butanol. A mixture of isobutyraldehyde, 18.2 ml (0.20 M) and diethyl succinate 41.55 ml (0.25 M) was added to the t-butanol solution over 30 min. The reaction mixture was stirred under reflux, for 2 h. The solvent was removed from the reaction mixture by evaporation under reduced pressure and acidified with 2N HCl. The product was extracted with ethyl ether, Et₂O (3 x 200 ml). The ether solution was washed with water (3 x 200 ml); and the product was extracted with 10% Na₂CO₃ (4 x 200 ml). The solution was acidified with conc. HCl solution and the product was isolated by extraction with Et₂O (4 x 150 ml). The ether layer was washed with water, dried over sodium sulfate, and evaporated. The remaining oil was dissolved in ethanol (300 ml) and hydrogenated in the presence of 10% palladium on charcoal (3.0 g). The resultant mixture was filtered through Celite and the solvent was evaporated to yield 38.04 g 2-carboethoxycarbonyl-4-methyl pentanoic acid as a mixture of isomers in the form of an oil. The isolated monoethyl ester was further purified on silica gel by flash chromatography using as eluent mixture ethyl acetate: hexane:acetic acid (1:10:0.05, v/v).

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1 NMR:

(300 MHz, CDCl₃): δ (ppm) 0.90 (6H, q, (CH₃)₂CH); 1.20-1.38 (4H, m, CH₃ ester + (CH₃)₂CH); 1.56 (2H, m, CH₂-CH); 2.45 and 2.72 (2H, dd and q, HOOC-CH₂); 2.84 (1H, m, CH₂-CH-CO); 4.14 (2H, q, CH₂ ester).

5 B. 2-Carbo-t-butoxycarbonyl-4-methylpentanoic acid

To a chilled (-70°) solution of 3-(ethoxycarbonyl)-3-(2-methylpropyl)propanoic acid (23.0 g) in 200 ml of methylene chloride was added isobutylene, 200 ml and conc. sulfuric acid (4 ml). The reaction mixture was stirred in a glass medium pressure reaction vessel for 4 days at RT. Then the solution was cooled to -70°C, opened, and saturated NaHCO₃ solution was added (80 ml). The remaining solvents were evaporated and product was extracted with ethyl ether (3 x 200 ml). The ether solution was washed with H₂O, dried over Na₂SO₄, and evaporated to yield the diester (29.48 g) as an oil. Diester (29.48 g) was hydrolyzed with 2N NaOH (40.5 ml) in 300 ml 50% aqueous ethanol for 12 h at RT. Then ethanol was evaporated and remaining oil was diluted with water and extracted with ethyl ether (3 x 200 ml). The aqueous solution was acidified with 2N HCl to pH = 2 and product was taken into Et₂O and gave after evaporation of solvent, 15.83 g of product as an oil. The obtained monoester was purified on silica gel by flash chromatography using as eluent ethyl acetate:hexane:acetic acid (1:9:0.1, v/v).

NMR

(300 MHz, CDCl₃): δ (ppm) 0.90 (6H, q, (CH₃)₂-CH); 1.27 (1H, m, (CH₃)₂CH); 1.41 (9H, s, (CH₃)₃-C); 1.60 (2H, m, (CH₃)₂CH-CH₂); 2.34 and 2.55 (1H and 1H; dd and q, CO-CH₂-CH); 2.82 (1H, m, CH-COOH).

1 C. Preparation of HO-NH-CO-CH₂-CH(CH₂CH(CH₃)₂)-CO-Nal-
2 Ala-NH₂

To the chilled (0°C) solution of t-butyl ester
(0.512 g) and L-naphtylalanyl-L-alanine amide
5 hydrochloride (0.808 g) in dimethylformamide was added
triethylamine (0.42 ml) and then slowly by parts N-
ethyl-N'-(3-dimethyl amino propyl) carbodiimide (0.479
g) over 15 min. The reaction mixture was stirred for 2
h at 0°C and overnight at RT. The next day, ethyl
10 acetate (100 ml) was added and the solution was washed
three times with 50 ml portions of 1N HCl, NaHCO₃(sat),
brine, and dried over magnesium sulfate. A white solid
material (0.44 g) obtained after evaporation of solvent,
was treated with 6N HCl/dioxane at RT for 60 min to
15 remove the t-butyl ester group. Evaporation of dioxane
and precipitation with ethyl ether gave a white solid
product (0.320 g) which was then coupled to O-benzyl
hydroxylamine again using the EDC procedure with
triethylamine as listed above. Catalytic hydrogenation
(10% Pd/C, MeOH, 4 h) was used to remove the benzyl
20 protecting group, giving the hydroxamic acid product as
a mixture of two diastereoisomers. The isomers were
isolated using reversed phase chromatography on a C-18
Dynamax column using an isocratic TFA/AcCN elution
mixture. The final products were lyophilized and
25 characterized as specified below.

NMR (ISOMER I):

(300 MHz, DMSO-d₆):δ(ppm) 0.64 and 0.73 (6H,
2xd, (CH₃)₂CH); 0.90 (3H, m, (CH₃)₂-CH-CH₂ and (CH₃)₂-
30 CH-CH₂); 1.22 (3H, d, CH₃-CH); 2.64 and 3.00 (1H and 1H,
m, CH₂-C₁₀H₇); 1.84-1.96 (3H, m, CO-CH₂-CH); 4.20 (1H,
m, CH-CH₂C₁₀H₇); 4.56 (1H, m, CH-CH₃); 6.98 and 7.21 (1H
and 1H, s, CO-NH₂); 7.40-7.90 (8H, m, C₁₀H₇ and CH₂-CH-

1 CO-NH-); 8.18 (1H, d, CO-NH-CH-CH₃); 8.66 (1H, s, NH-OH); 10.32 (1H, s, NH-OH).

HPLC (ISOMER I):

5 Rt = 13.5 min, Hibar C18 (4 .7 x 150 mm),
gradient 30-60% B in 30 min, A: 0.05% aqueous TFA; B:
0.05% TFA in AcCN, 1 ml/min.

NMR (ISOMER II):

(300 MHz DMSO-d₆):δ(ppm) 0.24 (3H, d,
(CH₃)₂CH); 0.38 (4H, m, (CH₃)₂CH and (CH₃)₂CH); 0.70 and
10 1.08 (1H and 1H, m, (CH₃)₂-CH-CH₂); 1.34 (3H, d, CH₃-
CH); 1.92 and 2.02 (1H and 1H, m, CO-CH₂-CH); 2.86 and
3.34 (1H and 1H, m, CH₂-C₁₀H₇); 2.47 (1H, m, CH₂-CH-CO);
4.23 (1H, m, CH₂C₁₀H₇); 4.55 (1H, m, CH-CH₃); 7.02 and
7.15 (1H and 1H, s, CO-NH₂); 7.44-7.78 (7H, m, C₁₀H₇);
15 8.00 (1H, d, CH₂CO-NH-); 8.42(1H, d, CO-NH-CH-CH₃); 8.68
(1H, s, NH-OH); 10.50(1H, s, NH-OH).

HPLC (ISOMER II):

20 Rt = 15.9 min, Hibar C18 (4.7 x 150 mm),
gradient 30-60% B in 30 min, A: 0.05% aqueous TFA; B:
0.05% TFA in AcCN, 1 ml/min.

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EXAMPLE II

1 Preparation of HO-NH-CO-CH₂-CH(CH₂CH(CH₃)₂)-CO-Nal-Pro-
2 NH₂

To a chilled (0°C) solution of
3 naphthylalanylalanine hydrochloride (0.50 g), t-butyl
5 ester (0.3 g), N-hydroxy-benzotriazole (0.22 g), and BOP
(0.67 g) in DMF was added triethylamine (0.6 ml). The
reaction mixture was stirred for 1 h at 0°C and for 16 h
at RT. Then the reaction mixture was diluted with AcOEt
10 (100 ml), washed with 3 x 1 N HCl, 3 x NaHCO₃(sat),
brine, and dried over MgSO₄. Crude product was purified
by flash chromatography on silica gel using solvent
system AcOEt:AcOH(100:1 v/v). After evaporation of the
solvent, the major fraction gave 0.6 g of solid product.
15 Removal of t-butyl ester from succinyldipeptide was
carried out by 10 N solution of HCl/dioxane.
Evaporation of dioxane and precipitation with diethyl
ether gave 0.52 g of product which was further coupled
to O-benzylhydroxylamine using EDC method in the
presence of Et₃N as described in Example I. The
20 resulting product was hydrogenated (10% Pd/C, MeOH 6 h)
to remove benzyl protecting group. Hydroxamic acid was
obtained as a mixture of two diastereoisomers. The
isomers were isolated using preparative reversed phase
chromatography as described in Example I. Final
25 products were lyophilized and characterized as specified
below:

Isomer I

HPLC: R_f = 6.92 min, Vydac C₁₈(218TP54, 4.6 x
250 mm), gradient 30→60% B in 30 min, 1 ml/min. A: 0.05%
30 aqueous TFA; B: 0.05% TFA in AcCN. FAB-MS: cal. 482;
found MH+483, M+Na⁺ 505

1 Isomer II

HPLC: $R_f = 10.43$ min, Vydac 98(218TP54, 4.6 x 250 mm), gradient 30→60% B in 30 min, 1 ml/min. A: 0.05% aqueous TFA; B: 0.05% TFA in AcCN FAB-MS: calc., MW=482;
5 found $M+H^+$ 483; $M+NA^+$ 503

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EXAMPLE III

1 Preparation of HO-NH-CO-CH(CH₃)-CH(CH₂-CH(CH₃)₂)-CO-Nal-
2 Ala-NH₂

4-methyl-2-oxopentanoic acid benzyl ester (1)

5 To the cooled solution of 4-methyl-2-oxo-
pentanoic acid (10 g), benzyl alcohol (9.56 g) and 4-
methyl aminopyridine (0.93 g) in 50 ml of methylene
chloride was added slowly N-ethyl-N'-(3-
dimethylaminopropyl) carbodiimide over 30 min. The
10 reaction mixture was stirred 1 h at 0°C and overnight at
RT. The next day, CH₂Cl₂ was evaporated, the oily
residue was dissolved in 200 ml ethyl acetate and washed
three times with one of the following: 1 N HCL, 10%
Na₂CO₃, brine, then dried over MgSO₄. The crude
15 compound (19.19 g) after evaporation of AcOEt was
purified by flash chromatography on silica gel using
ethyl acetate/hexane mixture as eluent. After
evaporation of the solvents, the major fraction gave
13.26 g of oily product.

NMR(300 MHz, CDCl₃)

20 δ(ppm): 0.96(6H,d,(CH₃)₂-CH); 2.20 (1H,m,(CH₃)₂CH); 2.74
(2H,d,CH₂-CH); 5.28(2H,s,CH₂-C₆H₅), 7.40 (5H,m,C₆H₅).

2-(1'-Ethoxycarbonyl ethyl)-4-methylpentanoic acid)(2)

25 Triethylphosphorus propionate (5.975 g,25 mM)
was added into suspension of sodium hydride (80% mineral
oil suspension) 0.75 g in 100 ml of dry toluene at room
temperature. The reaction mixture was heated up to 50-
60°C until sodium hydride was dissolved. Then the
reaction mixture was cooled to -70°C and benzyl 4-
30 methyl-2-oxopentanoate 5.0 g (38 mM) was added and the
resulting mixture was allowed to warm up to room
temperature and was stirred for an additional 1 h at RT.

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1 The toluene solution was washed with 10% citric acid 3
x, water (3 x), and dried over MgSO_4 . The obtained oil
(7.01 g) was hydrogenated in 300 ml of EtOH in the
presence of 1 g of 10% palladium/carbon for 96 h. Then
5 the catalyst was filtered and the solvent was removed
under reduced pressure. The crude product (4.8 g) was
purified by flash chromatography on silica gel using a
mixture of AcOEt/hexane/AcOH(1:3:0.01 v/v) as an eluent.
Major fraction (2.26 g) was obtained after evaporation
of solvents.

10 NMR (300MHz, CDCl_3)

δ (ppm): 0.86(6H, M, $(\text{CH}_3)_2\text{C}$); 1.18(3H and 1H, d and m, CH_3 -
CH and $(\text{CH}_3)_2\text{CH}$); 1.23(3H, t, CH_3 ester) 1.60(2H, m, CH_2 -
CH); 2.68(1H+1H, m+m, $\text{CH}-\text{CH}$); 4.12(2H, q, CH_2 ester).

15 $\text{HO}-\text{NH}-\text{CO}-\text{CH}(\text{CH}_3)-\text{CH}(\text{CH}_2-\text{CH}(\text{CH}_3)_2)-\text{CO}-\text{Nal}-\text{Ala}-\text{NH}_2$

To the cooled solution (0°C) of monoethyl
ester (1.08 g), naphthylalanylalanine amide hydrochloride
(1.67 g and (benzotriazolyloxy) tris-(dimethylamino)
20 phosphonium hexafluorophosphate (BOP) 2.21 g in 5 ml of
DMF was added triethylamine (2.1 cm^3). The reaction
mixture was stirred for 2 h at 0°C and overnight at RT.
Then the reaction mixture was diluted with ethyl acetate
(100 ml) and washed three times with the following: 1N
HCl, NaHCO_3 (sat), brine, and dried over MgSO_4 . A white
25 solid material (0.65 g) obtained after evaporation of
AcOEt and precipitation with hexane was saponified with
1N NaOH in methanol/water solution. The resulting
product (0.52 g) was coupled into O-benzyl hydroxylamine
using EDC procedure with Et_3N as described above for
30 example I. Catalytic hydrogenation (10% Pd/carbon,
MeOH, 4h) was used to remove the benzyl protecting
group, giving hydroxamic acid product as mixture of four

1 isomers. The isomers were isolated using reversed phase chromatography on C₈-Dynamax column using an isocratic elution with AcCN:H₂O:TFA (39:61:0.1 v/v). Final products were lyophilized and characterized as specified below:

5 Isomer I

NMR(300 MHz in DMSO-d₆): δ(ppm): 0.18(3H, s, (CH₃)₂CH-); 0.32(4H, bs, (CH₃)₂CH- and (CH₃)₂CH-); 0.64 and 1.12(1H and 1H, m and m, (CH₃)₂-CH-CH₂); 0.90(3H, d, CH₃-CH); 1.26(3H, d, CH₃-CH-CONH₂); 2.06(1H, m, CH₃CH); 10 2.32(1H, m, (CH₃)₂CH-CH₂-CH); 2.92 and 3.24 (1H and 1H, m and m, CH₂-C₁₀H₇); 4.26(1H, m, CH-CH₂-C₁₀H₇) 4.62(1H, m, CH₃-CH); 7.00 and 7.28(1H and 1H, s and s, CO-NH₂); 7.46-7.84 (8H, m, C₁₀H₇ and NH-CH-CH₂-C₁₀H₇); 8.36(1H, d, CH₃CH-NH); 8.66(1H, 6s, NH-OH); 10.38 (1H, s, 15 NH-OH).

HPLC: R_f=7.67 min, Vydac C₁₈(218TP54, 4.6 x 250 mm), gradient 30→60%B in 30 min, 1 ml/min. A: 0.05% aqueous TFA; B: 0.05% TFA in AcCN

FAB-MS: calc. 470; M+H⁺ = 471; M+Na⁺=493.

20 Isomer II

NMR(300MHz in DMSO-d₆): δ(ppm): 0.64(9H, m, (CH₃)₂CH and CH₃CH); 0.92(1H, m, (CH₃)₂CH); 1.34 and 1.14(1H and 1H, m and m, (CH₃)₂-CH-CH₂); 1.20 (3H, d, CH₃-CH-CONH₂); 2.18(1H, m, CH₃-CH); 2.40(1H, m, (CH₃)₂-CH-CH₂-CH); 2.96 and 25 3.22(2H, m, CH₂-C₁₀H₇); 4.20(1H, m, CH-CH₂C₁₀H₇); 4.66(1H, m, CH₃CH-CONH₂); 6.96 and 7.22(1H and 1H, s and s, CONH₂); 7.42-7.80(7H, m, C₁₀H₇); 7.96(1H, d, NH-CH-CH₂-C₁₀H₇); 8.16(1H, d, CH₃-CH-NH); 8.66(1H, bs, NH-OH); 10.32(1H, s, NH-OH);

30 HPLC: R_f=7.89 min; Vydac C₁₈(218TP54, 4.6 x 250 mm), gradient 30→60%B in 30 min, 1ml/min. A: 0.05% aqueous TFA; B: 0.05% TFA in AcCN

1 FAB-MS: calc. 470; found $M+H^+=471$; $M+Na^+=493$.

Isomer III

NMR: δ (ppm): 0.76(9H,m,(CH₃)₂CHCH₂ and CH₃-CH);
1.04(1H,m,(CH₃)₂CH-CH₂) 1.24(1H,m,(CH₃)₂CH-CH₂);
5 1.34(4H,bd,CH₃-CH and (CH₃)₂CHCH₂); 2.08(1H,m,CH₃-CH);
2.40(1H,m,(CH₃)₂CHCH₂CH); 2.86 and 3.18(1H and 1H,m,CH₂-
C₁₀H₇); 4.24(1H,m,CH-CH₂-C₁₀H₇); 4.48(1H,m,CH₃-CH);
7.10(1H,s,CONH₂); 7.40-7.80(8H,m,C₁₀H₇ and CONH₂);
7.80(1H,d,NH-CH-CH₂-C₁₀H₇); 8.28(1H,d,NH-CH-CH₃);
8.66(1H,s,NH-OH); 10.56(1H,s,NH-OH).

10 HPLC: R_f=11.84, Vydac C₁₈(218TP54, 4.6 x 250 mm),
gradient 30→60%B in 30 min, 1 ml/min. A: 0.05% aqueous
TFA;B: 0.05% TFA;B: 0.05% TFA in AcCN FAB-MS calc. 470;
found $M+H^+=471$; $m+Na^+=493$.

Isomer IV

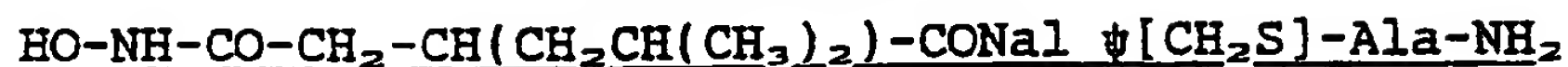
15 NMR: δ (ppm): 0.08(4H,m,CH₃)₂CH and (CH₃)₂CH-);
0.40(2H,d,(CH₃)₂CH); 0.82 and 1.02(1H and 1H,m,(CH₃)₂CH-
CH₂); 0.96(3H,d,CH₃-CH); 1.42(3H,d,CH₃-CH-CONH₂);
2.08(1H,m,CH₃-CH); 2.26(1H,m,(CH₃)₂CH-CH₂-CH);
2.80(1H,m,CH₂-C₁₀H₇); 4.28(1H,m,CH-CH₂-C₁₀H₇);
20 4.56(1H,m,CH₃-CH); 7.22(1H,s,CONH₂); 7.38-7.82(9H,m,C₁₀H₇
and NH-CH-CH₂-C₁₀H₇ and CONH₂); 8.38(1H,d,CH₃-CH-NH);
8.78(1H,bs,NH-OH); 10.62(1H,s,NH-OH).

HPLC: R_f=12.82 min, Vydac C₁₈(218TP54, 4.6 x 250 mm),
gradient 30→60%B in 30 min, 1 ml/min. A: 0.05% aqueous
25 TFA;B: 0.05% TFA in AcCN.

FAB-MS: calc. 470; found $M+H^+=471$, $M+Na^+=493$.

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EXAMPLE IVPreparation of

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A. H-Nal-CH₂OH. L-naphthylalanine-methyl ester
hydrochloride (4.0g; 15 mmol) was suspended in CHCl₃ (60
5 ml) and an excess of solution of NH₃ in CHCl₃ was
carefully added. The mixture was stirred at room
temperature for 15 minutes, then the NH₄Cl formed was
filtered. The white oil residue was dissolved in
10 anhydrous ether (100ml) and added, dropwise, to a
suspension of LiAlH₄ (0.76 g; 20 mmol) in ether (60ml).
After complete addition, the reaction was stirred at
room temperature for 3h. Water was added and the pH was
adjusted to 10 with 2 N NaOH, then the product was
15 extracted with ether (60 ml). The organic layer was
washed with water, dried over Na₂SO₄, filtered and
evaporated. The product was collected as a yellowish
solid (2.76 g; 91% yield): mp 98-100°C.

20 B. Boc-Nal-CH₂OH. L-naphthylalaninol (2.72 g; 13.5
mmol) was dissolved in tert-butanol (60 ml) and di-t-
butyl pyrocarbonate (3.16 g; 14.5 mmol) was added. The
reaction was stirred at room temperature for 3 h, then
the solvent was removed in vacuo. A white solid was
crystallized from AcOE/hexane (3.47 g; 92% yield): mp
25 131-132°C.

C. Boc-Nal-CH₂OTs. N-t-
butyloxycarbonylnaphthylalaninol (3.71 g; 12.3 mmol) was
dissolved in pyridine (15 ml) and the solution was
30 cooled to -30°C. Tosyl chloride (2.36 g; 12.4 mmol) was
added and the mixture was stirred to clearness at -30°C.
and then put into the refrigerator overnight. Pyridine

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1 was removed in vacuo and the product was extracted with
either (4 x 30 ml). The organic layer was washed with 1
N HCl(2 x 30 ml), H₂O(1 x 30ml), H₂O(1 x 30 ml), NaHCO₃
5 5%(2 x 30 ml) and saturated NaCl(1 x 30 ml), then dried
over Na₂SO₄, filtered and stripped to leave an oily
residue which was crystallized from AcOEt/hexane (4.6 g;
82% yield).

D. D-2-Br-propionic acid. D-Ala (4.45 g; 50 mmol) and
KBr (24g; 200 mmol) were dissolved in 2.5 N H₂SO₄
(150ml) and the solution was cooled to -5°C. NaNO₂ (7.6
10 g; 110 mmol) dissolved in water (30 ml) was added,
dropwise, over a period of 1 h and after this time the
reaction was stirred at 0°C for 1 h and at room
temperature for 5 h. The produce was extracted with
ether (3 x 50 ml) and the organic solution was washed
15 with H₂O and saturated NaCl, then dried over Na₂SO₄,
filtered and stripped to a yellowish oil. The oil was
distilled in vacuo, yielding a colorless oily product
(3.73 g; 54% yield).

E. L-2-thio-propionic acid. The product of D (5.87 g;
20 38 mmol) was added, dropwise, to a solution of sodium
thiocarbonate in water (25 ml; 33% v/v) and cooled to
0°C for 2 h and at room temperature for 5 days. After
this time, the solution was carefully acidified to pH 2
with 10 N H₂SO₄ and the product was extracted with ether
25 (4 x 50 ml). The organic layer was washed with H₂O,
dried over Na₂SO₄, filtered and evaporated in vacuo.
The oily residue was distilled in vacuo, yielding a
colorless oil (3.0 g; 76% yield).

F. Boc-Nalψ[CH₂S]Ala-OH. In a 3-neck round bottom
30 flask were placed absolute ethanol (30 ml) and sodium
(0.23 g; 10 mmol). Nitrogen was bubbled into the flask
and then 10 (0.53 g; 5 mmol) in ethanol (5 ml) was

1 added. The solvent was immediately removed in vacuo.
The solution of N-t-butylcarbonyl naphthylalanine
tosylate (2.46 g; 5.5 mmol) in DMSO (10 ml) was added to
the flask. The reaction was stirred at room temperature
5 for 6 h under a nitrogen blanket. NaHCO_3 5% (150 ml)
was added and the excess of Boc-Nal- CH_2OTs was extracted
with AcOEt. The aqueous layer was acidified to pH 2
with 2 N HCl, then extracted with AcOEt 94 x 50 ml).
The organic layer was washed with H_2O and saturated
10 NaCl, dried over Na_2SO_4 , filtered and stripped to leave
a crude solid which was crystallized from AcOEt/hexane
(1.4 g; 72% yield).

G. Boc-Nal ψ [CH_2S]Ala- NH_2 . Pseudopeptide Boc-
Nal ψ [CH_2S]Ala-OH (1.33 g; 3.4 mmol) was dissolved in THF
15 (25 ml) and the solution was cooled to -30°C . Et_3N (0.48
ml; 3.4 mmol) was added, followed by isobutyl
chloroformate (0.46 ml; 3.5 mmol). After 15 min an
excess of NH_3 in CHCl_3 was added and the reaction was
stirred for 30 min at -30°C and at room temperature for
3 h. The solvent was removed in vacuo and the residue
20 was dissolved in AcOEt (250 ml). The organic solution
was washed with H_2O (1 x 50 ml), NaHCO_3 5% (2 x 50 ml),
 H_2O (1 x 50 ml), 0.5 M citric acid (2 x 50 ml) and
saturated NaCl, then was dried over Na_2SO_4 and filtered.
After evaporation in vacuo of AcOEt, the residue was
25 crystallized from AcOEt/hexane (1.2 g; 90% yield).

H. HCl·H-Nal ψ [CH_2S]Ala- NH_2 . Pseudopeptide Boc-
Nal ψ [CH_2S]Ala- NH_2 (350 mg; 0.90 mmol) was dissolved in 4
N HCl/dioxane and stirred at room temperature for 10
min. The solvent was removed in vacuo over KOH
30 overnight, resulting in a thick, clear oil (280 mg; 96%
yield).

- 1 I. HOHNCO-CH₂-CH(CH₂CH(CH₃)₂)-CO-Nal [CH₂S]Ala-NH₂ The product prepared in H is coupled with the 2-carbo-t-butoxycarbonyl-4-methylpentanoic acid and deprotected in accordance with the procedure described in Example I.
- 5 The product thereof was reacted with O-benzyl hydroxylamine followed by catalytic hydrogenation using an excess of catalyst in accordance with the procedure in Example I to generate the above compound.

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EXAMPLE VPreparation of

HONHCO-CH₂-CH(CH₂CH(CH₃)₂)-CO-Nal ψ[CH₂NH]-Ala-NH₂

A. N-tert-butyloxycarbonyl-N,O-dimethyl-2-

5 naphthylalanine hydroxamic acid, (Boc-Nal-N(OMe)Me) 1

To a solution of N-tert-butyloxycarbonyl-2-naphthylalanine (1.58 g, 5 mmol) in DMF (10 ml) N,O-dimethylhydroxylamine hydrochloride (0.54 g, 5.5 mmol) was added. The solution was then cooled to 0°C and triethylamine (0.77 ml, 5.5 mmol) followed by EDC (1.05 g, 5.5 mmol) was added. The reaction mixture was stirred 2 h at 0°C and 16 h at room temperature. The solvent was removed in vacuo and residue was partitioned in a separatory funnel between ethyl acetate (70 ml) and 5% NaHCO₃ (20 ml). The organic layer was washed with 5% NaHCO₃ (2 x 20 ml), H₂O (1 x 20 ml), 1 N HCl (1 x 20 ml), H₂O (1 x 20 ml) and NaHCO₃ (1 x 20 ml), and brine (1 x 20 ml). The ethyl acetate fraction was then dried over Na₂SO₄ and stripped to leave slightly yellow solid. Crystallization from ethyl acetate/hexane gave 1 (1.27 g, 71%): R_f 0.80 (chloroform/methanol/acetic acid, 85:10:5), R_f 0.54 (ethyl acetate/hexane, 1:1); m.p. 98-100°C; H NMR (CDCl₃, 18°C) δ 1.36 (9H, s, C(CH₃)₃), 3.07 (2H, m, CH₂), 3.17 (3H, s, N-CH₃), 3.66 (3H, s, O-CH₃), 5.04 (1H, m, CH), 5.20 (1H, d, NH), 7.30-7.77 (7H, m, C₁₀H₇).

25 B. N-tert-butyloxycarbonyl-2-naphthylalanylψ[CH₂NH]
alanine amide (Boc-Nalψ[CH₂NH]Ala-NH₂ 2

a, N-tert-butyloxycarbonyl-2-naphthylalanal (Boc-
Nal-CHO)

30 To a cold (0°C, ice bath) solution of N-tert-butyloxycarbonyl-N,O-dimethyl-2-naphthylalanine hydroxamic acid (0.54 g, 1.5 mmol) in THF (10 ml) LiAlH₄ (0.14 g, 3.75 mmol) was added in portions over 15 min.

1 The resulting reaction mixture was stirred additionally
15 min at 0°C followed by addition of ethyl acetate (100
ml) and 10% citric acid (80 ml). After stirring 0.5 h
at 0°C, the layers were separated and the aqueous layer
5 was extracted with ethyl acetate (3 x 50 ml). The
organic fractions were pooled and washed with 5% NaHCO₃
(1 x 5 ml), H₂O (1 x 50 ml), 1 N HCL (1 x 50 ml) and
brine (1 x 50 ml), and dried over Na₂SO₄. Evaporation
of solvent yielded white powder (0.43 g, 99%):
10 R_F 0.74 (ethyl acetate/hexane, 1:1); R_F 0.58
(chloroform/methanol, 9:1), which was used immediately
in the next step.

b. N-tert-butyloxycarbonyl-2-naphthylalanylψ[CH₂NH]
15 alanine amide (Boc-Nalψ[CH₂NH]Ala-NH₂)₂

To a solution of N-tert-butyloxycarbonyl-2-
naphthylalanal (0.43 g, 1.47 mmol) in methanol (4 ml)
containing 3% acetic acid alanine amide hydrochloride
(0.19 g, 1.5 mmol) was added. To the resulting mixture
NaBH₃CN (0.12, 1.0 mmol) was added in portions over 0.5
20 h. After 2 h, when TLC (chloroform/methanol, 9:1)
didn't show any substrates, the reaction mixture was
partitioned in a separatory funnel between ethyl acetate
(70 ml) and 5% NaHCO₃ (30 ml), and the aqueous fraction
was extracted with ethyl acetate (3 x 20 ml). The
25 organic fractions were pooled, washed with 5% NaHCO₃ (1
x 20 ml) and brine (1 x 20 ml). The organic layer was
dried over Na₂SO₄, filtered and stripped to leave a
yellow solid. The crude pseudodipeptide was purified by
flash chromatography using 7% hexane in ethyl acetate.
30

Fractions containing the desired compound were
pooled and stripped to leave white powder.
Recrystallization from ethyl acetate/hexane gave

1 2(0.319, 57%): R_f 0.37 (chloroform/methanol, 9:1), R_f
 0.23 (chloroform/methanol/acetic acid, 85:10:5); m.p.
 141-143°C; analytical RP-HPLC (t_r =36.08 min, a linear
 gradient of 5-65% B over 60 min at a flow rate of 1.0
 5 ml/min); $^1\text{H-NMR}$ (CDCl_3 , 18°C) δ 1.29 (3 H, d, CH-CH_3); 1.38 (9
 H, s, $\text{C}(\text{CH}_3)_3$), 2.67 (2H, octet, $\text{C}_{10}\text{H}_7\text{-CH}_2$), 2.95 (2
 H, d, $\text{CH}_2\text{-NH}$), 3.11 (1 H, q, $\text{CH}_3\text{-CH}$), 4.05 (1H, m, NH-CH-CH_2),
 4.52 (1H, d, CO-NH-CH), 5.28 (1H, m, $\text{CH}_2\text{-NH-CH}$), 7.03-
 7.83 (9H, m, C_{10}H_7 and CONH_2).

10 c. 2-Naphthylalanyl ϕ [CH_2NH]alanine amide
 dihydrochloride(2 HCl x Na ϕ [CH_2NH]Ala-NH $_2$)3

Na-tert-butyloxycarbonyl protected compound,
2(0.19 g, 0.5 mmol) was placed in a round-bottom flask
 to which freshly prepared 4 N HCl.dioxane (15 ml) was
 added. The solution was stirred for 1 h. Evaporation
 15 of solvent in vacuo yielded white, very hygroscopic
 powder (0.17 g, 100%): R_f 0.22 (1-butanol/acetic
 acid/water, 4:1:1), R_f 0.05 (chloroform/methanol/acetic
 acid, 85:10:5) which was used immediately for the next
 step.

20 D. HONHCO-CH₂-CH(CH₂CH(CH₃)₂)CO-Na ϕ [CH₂NH]Ala-NH₂ 4

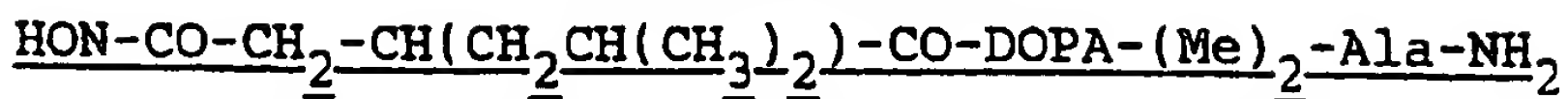
The product prepared in C is coupled with 2-
 carbo-t- butyloxy carbonyl-4-methyl pantanoic acid and
 deprotected in accordance with the procedure described
 in Example I. Then succinyl dipeptide is reacted with
 25 O-Benzyl hydroxylamine followed by catalytic
 hydrogenation as described in Example I giving mixture
 of two diastereoisomers of the above compound.

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EXAMPLE VI

Preparation of



A. L-3,4-dihydroxyphenylalanine methyl ester

5 hydrochloride, HCL·H-Dopa-OMe

To the cooled to -10°C suspension of L-3,4-dihydroxyphenylalanine in 30 ml of absolute methanol, thionyl chloride (2.6 ml, 36 mM) was added dropwise. The reaction mixture was stirred at room temperature for 48 h. Then, methanol was evaporated under reduced
10 pressure and the remaining residue was treated three times with ethyl ether evaporating after each time. Finally, the product was crystallized from the methanol/ethyl ether mixture, giving 7.43 g 100% white
15 crystalline substance.

NMR: (300 MHz, CDCl_3)

δ (ppm) 1.4(9H,s,(CH_3)₃-C); 2.05(2H,m, $\text{CH}_2\beta$); 3.70
(3H,s, CH_3 ester); 3.84 (6H, s, CH_3O); 4.54 (1H,m, $\text{CH}\alpha$),
4.95 (1H, m, NH); 6.62 (2H,d, CH_{arom}); 6.78(1H,d, CH_{arom}).

20 B. N-t-Butyloxycarbonyl-L-3,4-dihydroxyphenylalanine
methyl ester, Boc-Dopa-OMe

To a solution of L-3,4-dihydroxyphenylalanine methyl ester hydrochloride (7.43 g, 30 mM) and 4.2 ml 30 mM of triethylamine in 80 ml of t-butanol was added
25 portionwise di-t-butyl pyrocarbonate (6.5 g, 3mM). The reaction mixture was stirred for 1 h and then t-butanol was removed under reduced pressure. The remaining oily residue was dissolved in 250 ml of ethyl acetate and washed with 5% NaHCO_3 (3x), H_2O (1x), 0.5 M citric acid
(3x) and H_2O (1x), and dried over Na_2SO_4 . After removal
30 of the ethyl acetate, the compound was crystallized from the benzene giving 8.81 g (94%) white crystalline product. mp = $129-131^\circ\text{C}$.

1 C. N-t-butyloxycarbonyl-L-3,4-dimethoxyphenylalanine
methyl ester, Boc-Dopa(Me)₂-OMe

The mixture of Boc-Dopa-OMe (3.1 g, 10mM),
potassium carbonate (1.52 g, 11 mM), 18-crown-6 (291 mg,
1.1 mM), dimethylsulfate (1.05 ml, 11mM) in 10% DMF in
5 benzene was heated under reflux in a round bottom flask
equipped with azeotropic distilling receiver. After 4 h
of reflux, fresh portions of potassium carbonate (0.75
g, 5mM) and dimethyl sulfide (0.5 ml, 0.5 ml) were added
and the resulting reaction mixture was reflux for an
10 additional 4 h. Then the reaction mixture was cooled
and 100 ml of cold water was added. The organic layer
was washed 3 x with H₂O and dried over Na₂SO₄.
Crystallization from benzene gave 1.92 g (52%) solid
product.

15 mp = 109-111°C.

R_F = 0.84, (nBuOH:AcOH:H₂O, 4:1:1, v/v)

NMR (300 MHz, CCl₃)

δ(ppm) 1.4(9H, s(CH₃)₃-C); 2.05(2H, m, CH₂β); 3.70(3H, s, CH₃
ester); 3.84(6H, s, CH₃O-); 4.54(1H, m, CHα), 4.95(1H, s, NH);
20 6.62(2H, d, CH_{arom}); 6.78(1H, d, CH_{arom}).

D. N-t-butyloxycarbonyl-L-3,4-dimethoxyphenylalanine,
Boc-Dopa(Me)₂-OH

To a solution of Boc-Dopa(Me)₂-OMe(1.71 g, 4.6
mM) in 25 ml of MeOH was added 8 mM of NaOH in 5 ml of
25 water and the resulting mixture was stirred for 40 min.
Then methanol was evaporated under reduced pressure and
the remaining mixture was diluted with 80 ml of water.
The solution was acidified to pH = 2 in 1 N HCl and the
product was extracted with AcOEt (3 x 50 ml). Combined
30 ethyl acetate solution was washed twice with water and
then dried over NaSO₄, filtered and evaporated. The
oily residue was crystallized from ether/hexane giving
1.19 g white solid product.

mp = 140-147°C, TLC R_F = 0.94(CHCl₃:MeOH:AcOH, 85:10:5);

35 R_F = 0.81 (n-BuOH:AcOH:H₂O, 4:1:1, v/v)

1 NRM: (CDCl₃, 300 MHz)
δ(ppm): 1.42(9H,s,(CH₃)₃C); 3.1(2H,m,CH₂β);
3.84(6H,s,CH₃O); 4.58(1H,m,CH_α); 4.84(1H,d,NH);
6.76(4H,m,CH_{arom}).

5 E. Boc-Dopa(Me)₂-Ala-NH₂

To the chilled (0°C) solution of Boc-Dopa(Me)₂-OH(1.025 g)N-hydroxybenzotriazole (0.40 g) and alanine amide hydrochloride (0.385 g) in a mixture of dichloromethane/DMF(8:1 v/v) was added triethylamine (0.42 ml) and then portionwise N-ethyl-N¹-(3-dimethyl amino propyl) carbodiimide (0.575 g) over 30 min. The reaction mixture was stirred for 2 h at 0°C and overnight at RT. The next day, ethyl acetate (200 ml) was added and the solution was washed three times with 50 ml of 1 N HCl, NaHCO₃(sat), brine, and dried over Na₂SO₄. Evaporation of solvent gave 0.95 g of white material.

TLC: R_f = 0.92(CHCl₃:MeOH:AcOH, 85:10:5); R_f=0.79(n-BuOH:AcOH:H₂O, 4:1:1).

20 F. HCL·H-DOPA(Me)₂-Ala-NH₂

The product of E is dissolved in 4N-HCl/dioxane and stirred at room temperature for approximately 10-15 minutes. The solvent is removed in vacuo KOH overnight to form the above product.

H

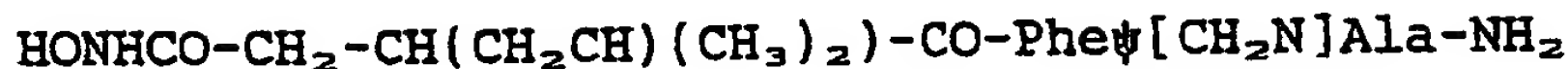
25 G. HON-COCH₂-CH(CH₂-CH(CH₃)₂)-CO-DOPA(Me)₂-Ala-NH₂

The product prepared in F is coupled with the 2-carbo-t-butoxycarbonyl-4-methyl pentanoic acid and deprotected in accordance with the procedure described in Example I. The product thereof is coupled with O-benzyl hydroxylamine followed by catalytic hydrogenation in accordance with the procedure described in Example I to give the above-identified compound.

EXAMPLE VII

Preparation of

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5 A α -tert-butyloxycarbonyl-N,O-dimethyl-phenylalanine hydroxamic acid (Boc-Phe-N(OMe)Me) 5

The title compound was synthesized from tert-butyloxycarbonyl-L-phenylalanine (2.65 g, 0.1 mmol) and N,O-dimethylhydroxylamine hydrochloride (1.07 g, 11 mmol) according to the procedure given for 1. The synthesis yielded compound 5 as an oil (2.48 g, 81%): R_f 0.40 (ethyl acetate/hexane, 1:1), R_f 0.78 (chloroform/methanol/acetic acid, 85:10:5); $^1\text{H-NMR}(\text{CDCl}_3, 17^\circ\text{C})\delta$ 1.38 (9H, s, $\text{C}(\text{CH}_3)_3$), 3.05 (2H, m, CH_2), 3.18 (3H, s, N- CH_3), 3.66 (3H, s, O- CH_3), 4.97 (1H, m, CH), 5.18 (1H, d(br.), NH), 7.17-7.28 (5H, m, C_6H_5).

15 B. N-tert-butyloxycarbonyl-phenylalanyl Ψ [CH_2NH]alanine amide (Boc-Phe Ψ [CH_2NH]Ala-NH $_2$) 6

a. N-tert-butyloxycarbonyl-phenylalanal (Boc-Phe-CHO)

20 The title aldehyde was synthesized from N-tert-butyloxycarbonyl-N,O-dimethyl-phenylalanine hydroxamic acid (0.92 g, 3 mmol) by reduction using LiAlH_4 (0.28 g, 7.5 mmol) according to the procedure given for 2. Evaporation of ethyl acetate yielded a white powder (0.55 g, 73%): R_f 0.70 (ethyl acetate/hexane, 1:2), R_f 0.53 (chloroform/methanol, 9:1), which was used immediately in the next step.

25 b. N-tert-butyloxycarbonyl-phenylalanyl Ψ [CH_2NH]alanine amide (Boc-Phe Ψ [CH_2NH]Ala-NH $_2$) 6

30 Compound 6 was prepared from N-tert-butyloxycarbonyl-phenylalanal (0.5 g, 2 mmol) and alanine amide hydrochloride (0.26 g, 2 mmol) by

1 following the procedure described for 2. Crude product
was purified by flash chromatography using ethyl acetate
as mobile phase.

Fractions containing the desired compound were
5 pooled and stripped to leave white powder.

Recrystallization from ethyl acetate/hexane gave 6 (0.39
g, 62%): R_f 0.30 (chloroform/methanol, 9:1), R_f 0.20
(chloroform/methanol/acetic acid, 85:10:5); m.p. 138-
140°C; analytical RP-HPLC (t_r =12.84 min, a linear
10 gradient of 20-60% B over 40 min at a flow rate of 1.0
ml/min); $^1\text{H-NMR}$ (CDCl_3 , 17°C) δ 1.25(3H, d, CH-CH_3 ,
1.37(9h, s, $\text{C}(\text{CH}_3)_3$), 2.58 (2H, octet, $\text{C}_6\text{H}_5\text{-CH}_2$), 2.75
(2H, d, $\text{CH}_2\text{-NH}$), 3.07 (1H, q, $\text{CH}_3\text{-CH}$), 4.00(1H, m, NH-CH-CH_2),
4.55(1H, d, CO-NH-CH), 5.41 (1H, s, $\text{CH}_2\text{-NH-CH}$), 7.02-
15 7.29(7H, m, C_6H_5 and CO-NH_2).

c. Phenylalanyl ψ [CH_2NH]alanine amide
dihydrochloride ($2\text{HCl} \times \text{Phe}\psi[\text{CH}_2\text{NH}]$) 7

N-tert-butyloxycarbonyl protection was removed
from N-tert-butyloxycarbonyl-phenylalanyl ψ [CH_2NH]alanine
amide (0.3 g, 0.95 mmol) using 4 N HCl/dioxane following
20 the procedure given for 3. Evaporation of solvents gave
white hygroscopic solid, 7 (0.28 g, 100%): R_f 0.20 (1-
butanol/acetic acid/water, 4:1:1), R_f 0.40
(chloroform/methanol/acetic acid, 85:10:5) which was
used immediately in the next step.

25 D. $\text{HONHCO-CH}_2\text{-CH}(\text{CH}_2\text{CH}(\text{CH}_3)_2)\text{-CO-Phe}$
 $\psi[\text{CH}_2\text{NH}]\text{Ala-NH}_2$

The product prepared in C is coupled with 2-
carbo-t-butyloxy-carbonyl-4-methyl pentanoic acid
followed by O-benzyl hydroxylamine and the product
30 hydrogenated in accordance with the procedure described
in Example 1.

EXAMPLE VIII

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Preparation of

 $\text{HONHCO-CH}_2\text{-CH(CH}_2\text{CH(CH}_3)_2\text{)-CO-Tyr(Me)}\psi[\text{CH}_2\text{NH}]\text{Ala-NH}_2$

5 A. $\text{Na-tert-butyloxycarbonyl-(N,O}^1\text{,O}^2\text{-trimethyl) tyrosine hydroxamic acid (Boc-Tyr(Me)-N(OMe)Me)}$ 9

The title compound was prepared from $\text{Na-tert-butyloxycarbonyl-(O-methyl)tyrosine}$ (2.95 g, 10 mmol) and $\text{N,O-dimethylhydroxylamine hydrochloride}$ (1.07 g, 11 mmol) by following the procedure given for 1.

10 Recrystallization from ethyl acetate/benzene/hexane gave white crystals (2.90 g, 85%): m.p. 59-61°C;

R_F 0.45 (ethyl acetate/hexane, 1:1), R_F 0.78 (chloroform/methanol/acetic acid, 85:10:5); $^1\text{H-}$

15 $\text{NMR(CDCl}_3\text{, 18}^\circ\text{C)}$ δ 1.38 (9H, s, $\text{C(CH}_3)_3$), 2.97 (2H, m, CH_2), 3.16 (3H, s, N-CH_3), 3.65 (3H, s, N-O-CH_3), 3.76 (3H, s, C-O-CH_3), 4.91 (1H, m, CH), 5.13 (1H, d, NH), 6.80-7.08 (4H, dd, C_6H_4).

B. $\text{N-tert-butyloxycarbonyl-(O-methyl)tyrosal}\psi$

20 $[\text{CH}_2\text{NH}]\text{alanine amide (Boc-Tyr(OMe)}\psi[\text{CH}_2\text{NH}]\text{Ala-NH}_2)$ 10

a. $\text{N-tert-butyloxycarbonyl-(O-methyl)tyrosal (Boc-Tyr(Me)-CHO)}$

The title compound was synthesized from $\text{Na-tert-butyloxycarbonyl-(N,O}^1\text{,O}^2\text{-trimethyl)tyrosine hydroxamic acid}$ (1.02 g, 3 mmol) and LiAlH_4 (0.28 g, 7.5 mmol) according to the procedure described for 2.

Evaporation of ethyl acetate gave white powder (0.80 g, 95%): R_F 0.72 (ethyl acetate/hexane, 1:1), R_F 0.55 (chloroform/methanol, 9:1), which was used immediately in the next step.

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1 B. N-tert-butyloxycarbonyl-(O-methyl)
tyrosylψ[CH₂NH]alanine amide (Boc-Tyr(OMe)ψ[CH₂NH]Ala-
NH₂) 10

Pseudodipeptide 10 was prepared from N-tert-
5 butyloxycarbonyl-O-methyl-tyrosal (0.8 g, 2.87 mmol)
alanine amide hydrochloride (0.32 g, 2.5 mmol) by
following the procedure given for 2. Crude product was
purified by flash chromatography using ethyl acetate as
mobile phase. Fractions containing the desired compound
10 were pooled and stripped to leave a white powder.
Recrystallization from ethyl acetate/hexane gave 10
(0.51 g, 59%): R_F 0.32 (chloroform/methanol, 9:1), R_F
0.21 (chloroform/methanol/acetic acid, 85:10:5); m.p.
122-124°C; analytical RP-HPLC (t_r=12.98, a linear
15 gradient of 20-60% B over 40 min at a flow rate of 1.0
ml/min); ¹H-NMR(CDCl₃, 18°C) δ 1.26 (3H, d, CH-CH₃),
1.38 (9H, s, C(CH₃)₃), 2.58 (2H, octet, C₆H₄-CH₂), 2.71
(2H, d, CH₂-NH), 3.08 (1H, q, CH₃-CH), 3.77 (3H, s, O-CH₃),
3.88 (1H, m, NH-CH-CH₂), 4.49 (1H, d, CO-NH-CH),
20 5.56 (1H, bs, CH₂-NH-CH), 6.80-7.24 (6H, m, C₆H₄ and CO-NH₂).

C. (O-Methyl)tyrosylψ[CH₂NH]alanine amide
dihydrochloride (2HCl x Tyr(OMe)ψ[CH₂NH]Ala-NH₂) 11

The title compound was synthesized from N-
tert-butyloxycarbonyl-(O-methyl)tyrosylψ[CH₂NH]alanine
25 amide (0.25 g, 0.71 mmol) using 4 N HCl/dioxane
according to the procedure described for 3. Evaporation
of solvents and drying in vacuo gave hygroscopic white
powder, 11 (0.23 g, 100%); R_F 0.20 (1-butanol/acetic
acid/water, 4:1:1), R_F 0.40 (chloroform/methanol/acetic
30 acid, 85:10:5), which was used immediately in the next
step.

1 D. $\text{HONHCO-CH}_2\text{-CH(CH}_2\text{CHCCH}_3)_2\text{-CO-}$
Tyr(Me) ψ [CH₂NH]Ala-NH₂

5 The product in C is coupled with 2-carbo t-
butyloxy-carbonyl-4-methyl pentanoic acid, folloed by O-
benzyl hydroxyl amine and the prodcut is hydrogenated in
accordance with the procedure described in Example I.

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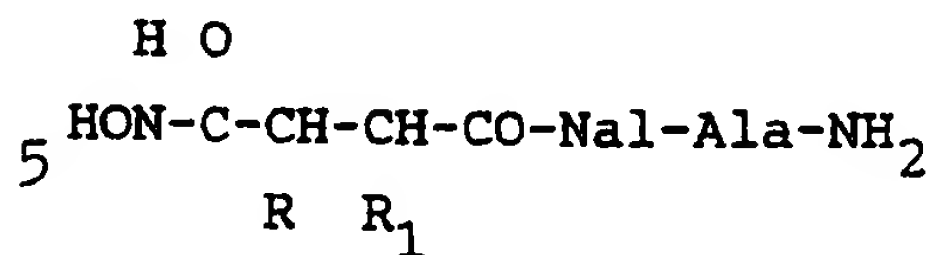
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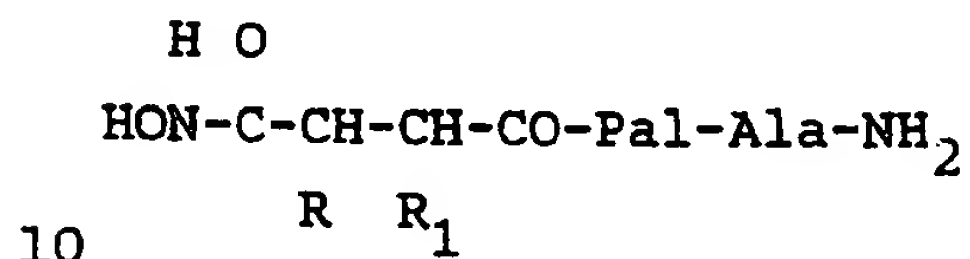
EXAMPLE IX

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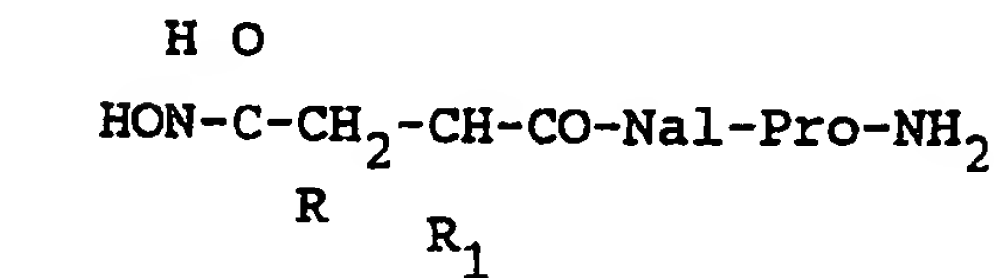
Using the procedures described herein, the following compounds can be prepared:



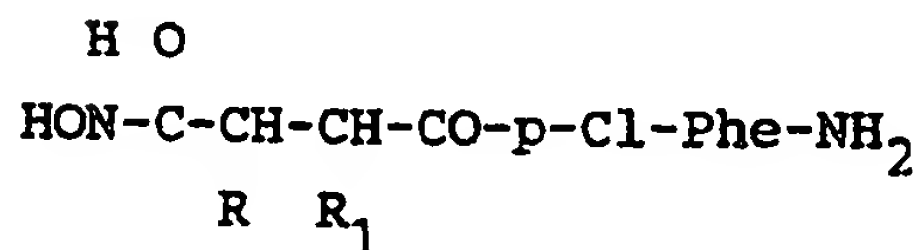
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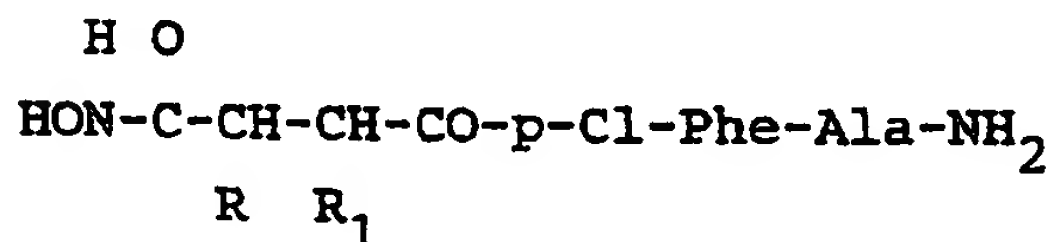
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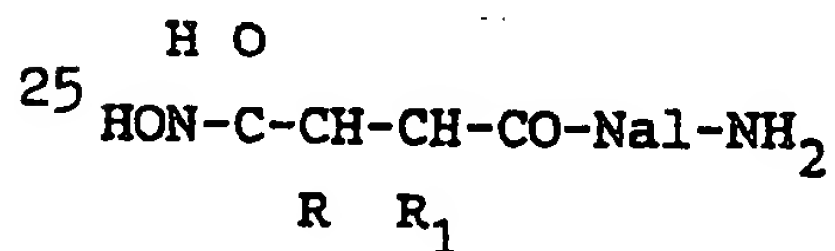
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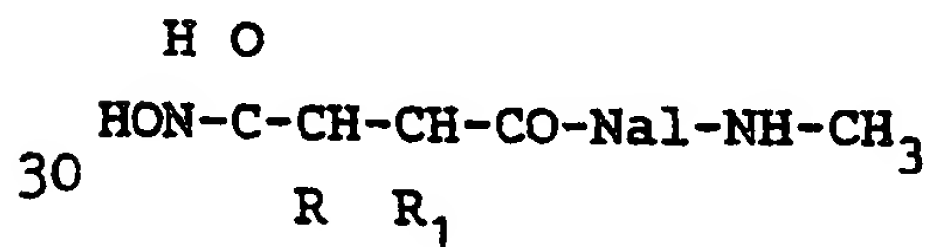
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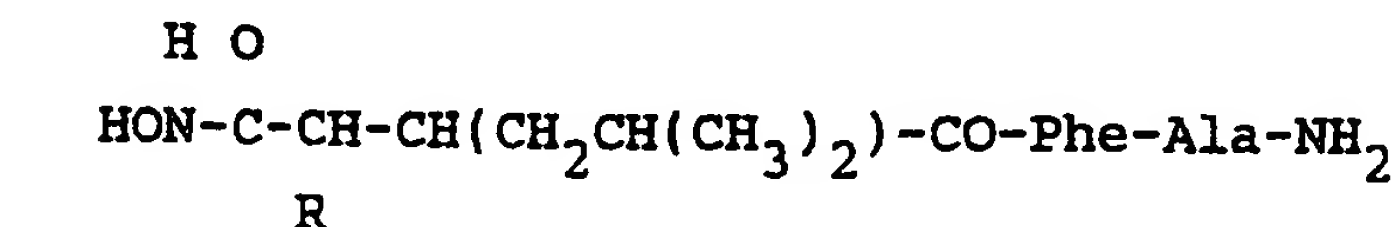
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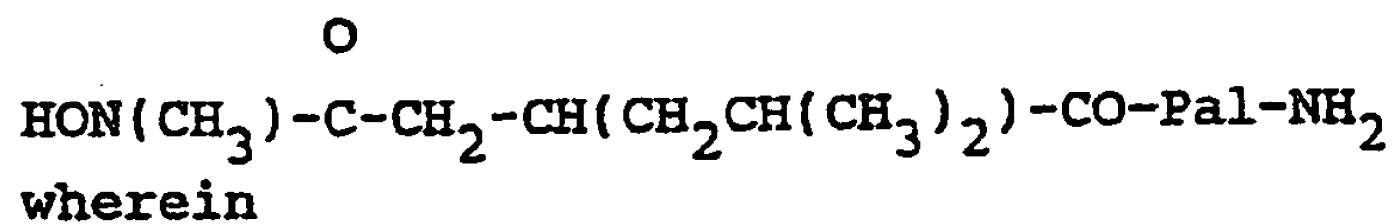
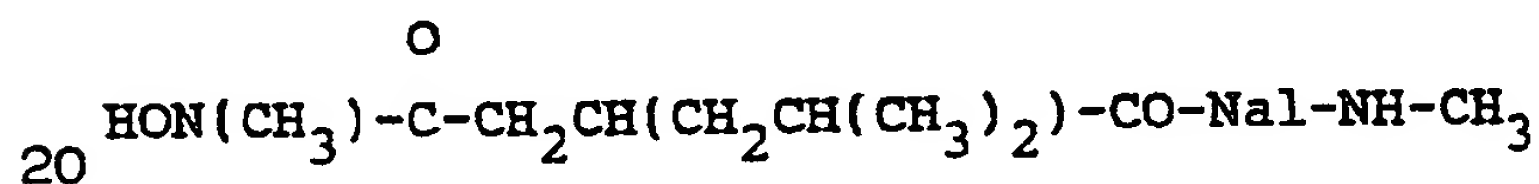
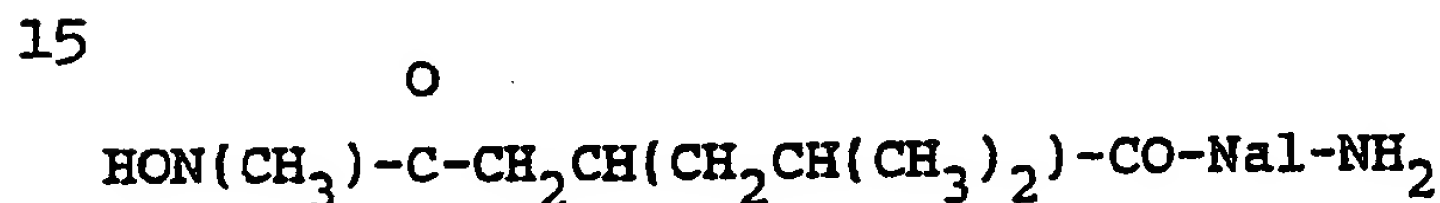
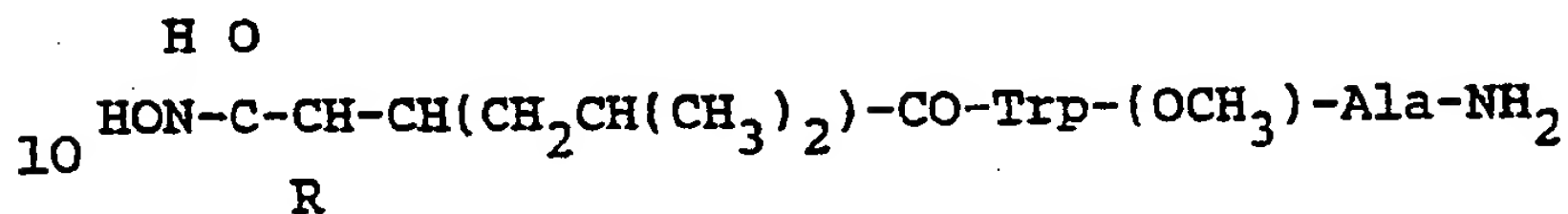
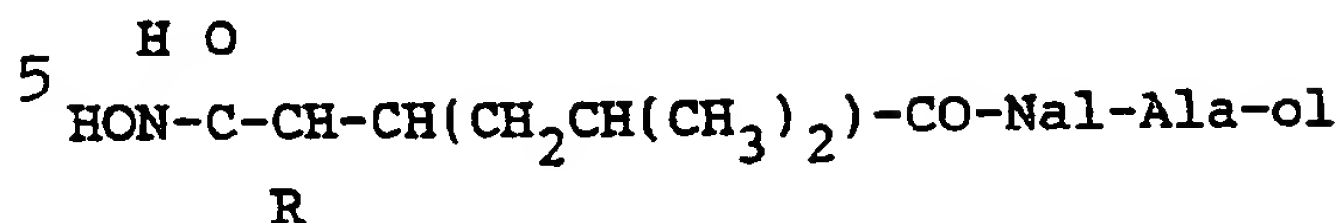
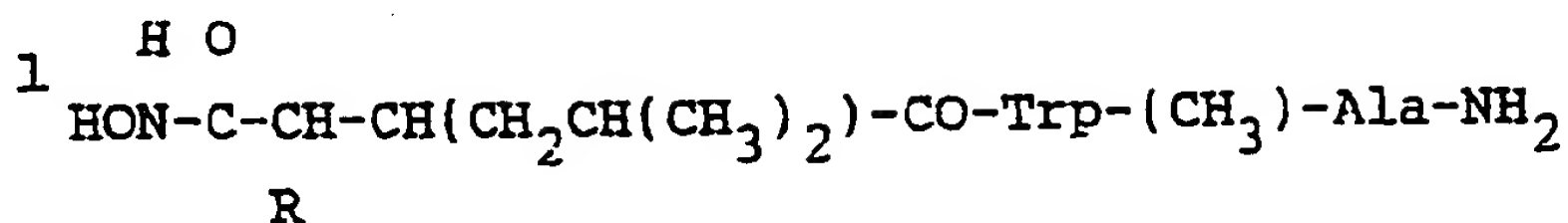
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- 25 Pal = 2, 3 or 4-pyridylalanine
Nal = 1- or 2-naphthylalanine
Trp(CH₃) = methyl substituted tryptophan
Trp(OCH₃) = methoxy substituted tryptophan
R₁ = CH₂CH(CH₃)₂ or CH(CH₃)CH₂CH₃
R = H or CH₃

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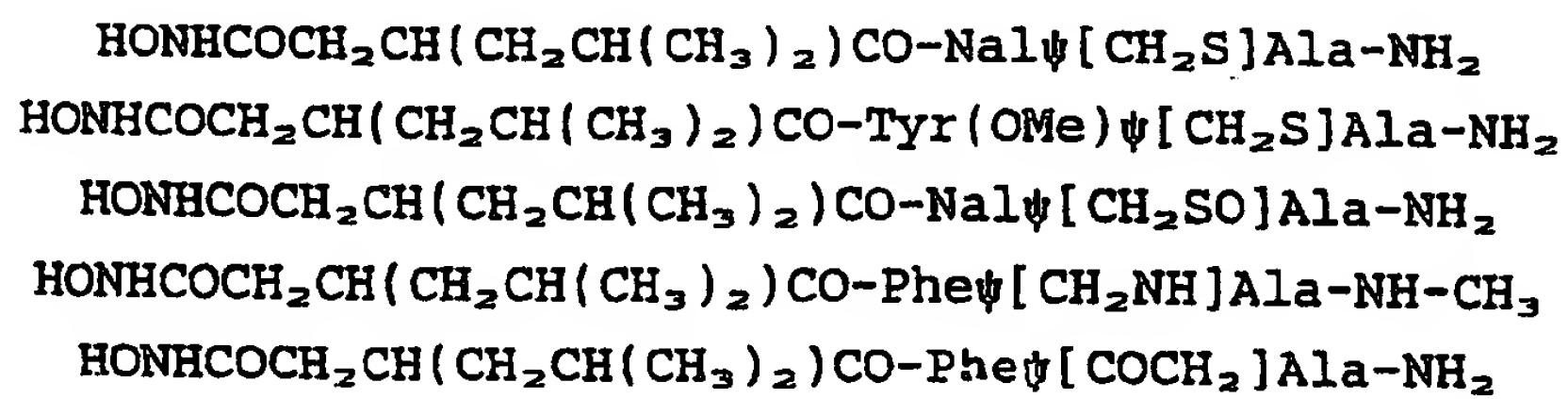
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EXAMPLE X

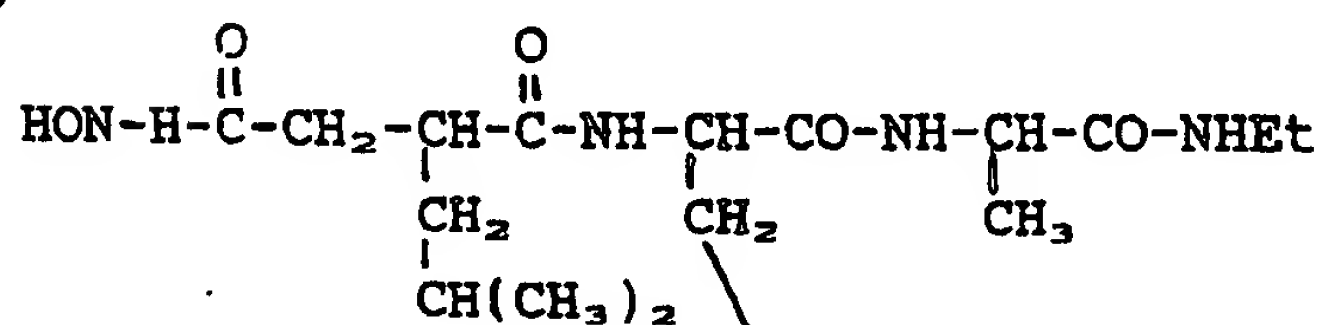
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Using the procedures described herein, the following compounds can also be prepared.

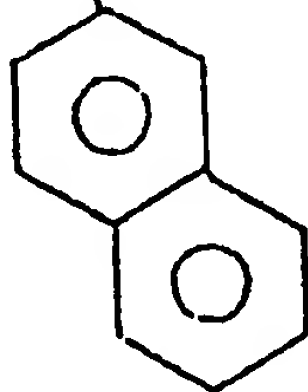
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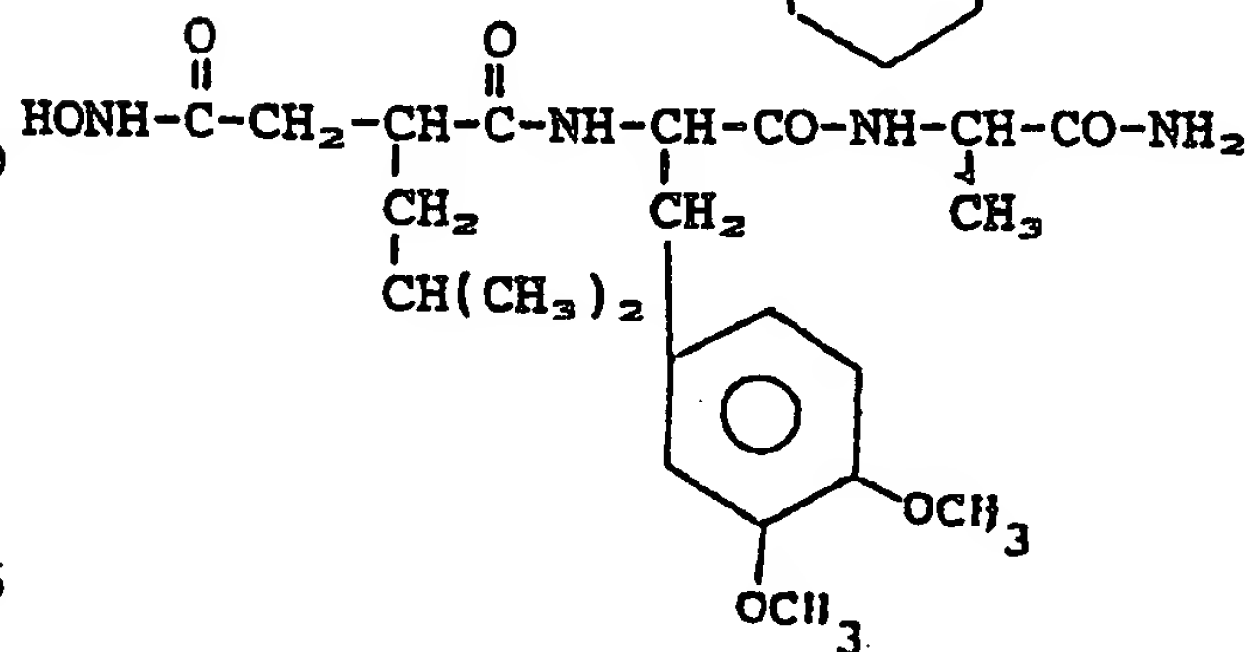
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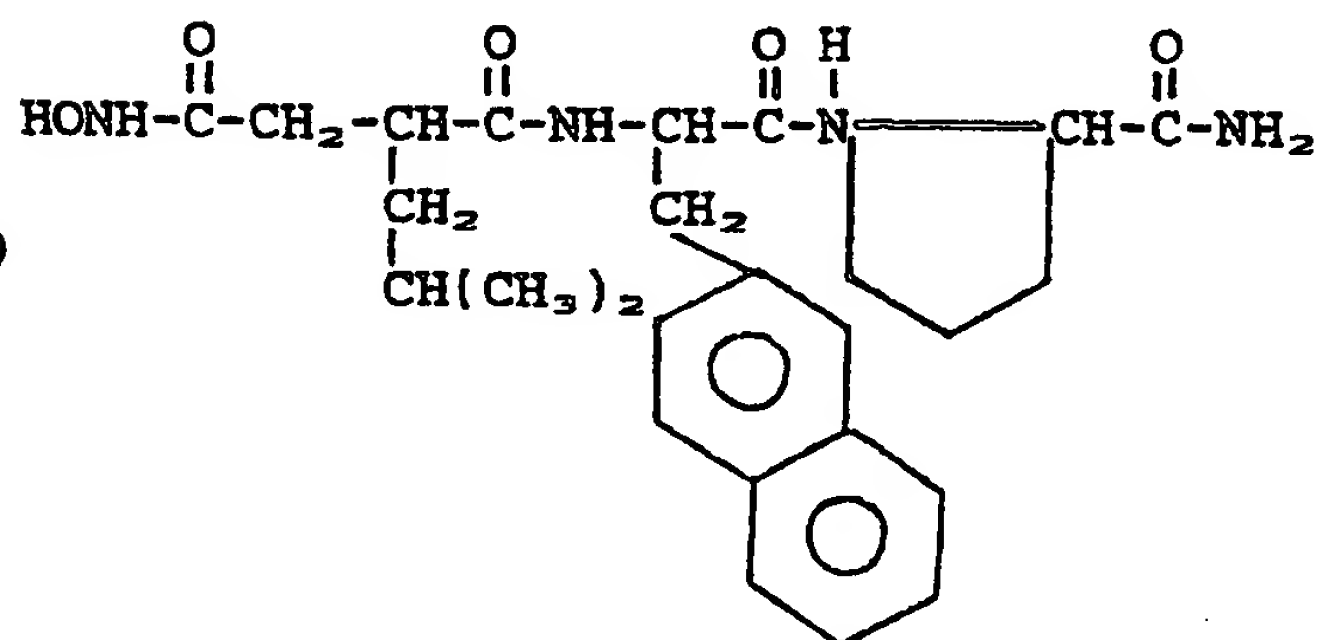


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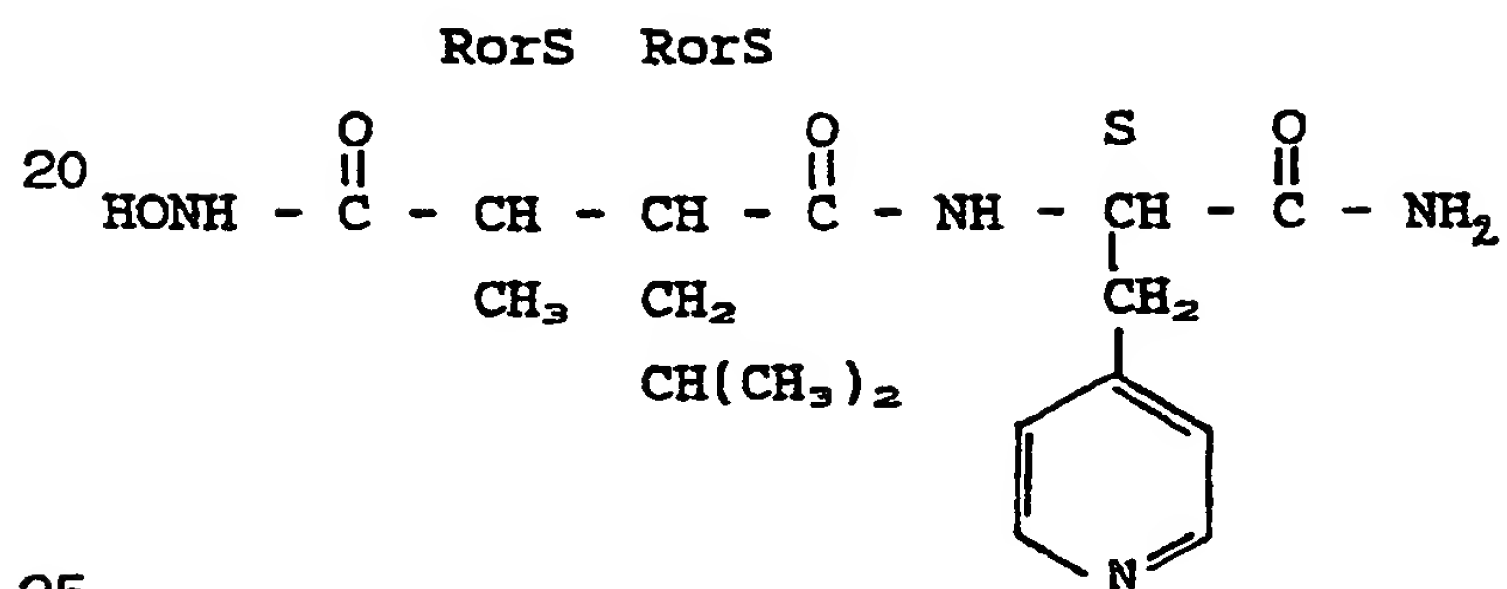
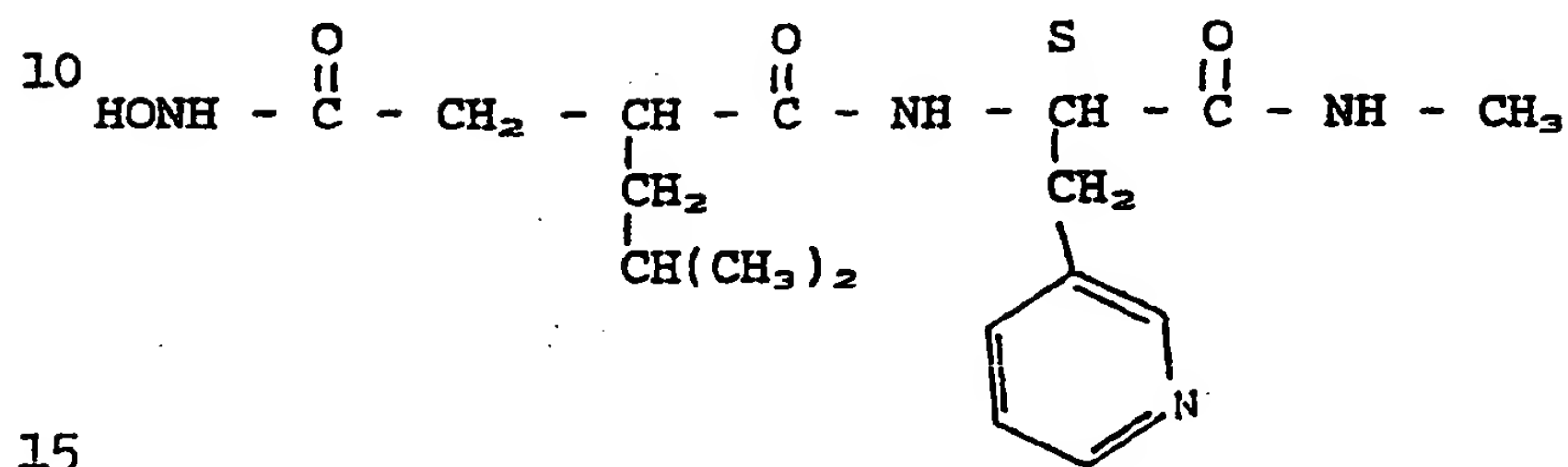
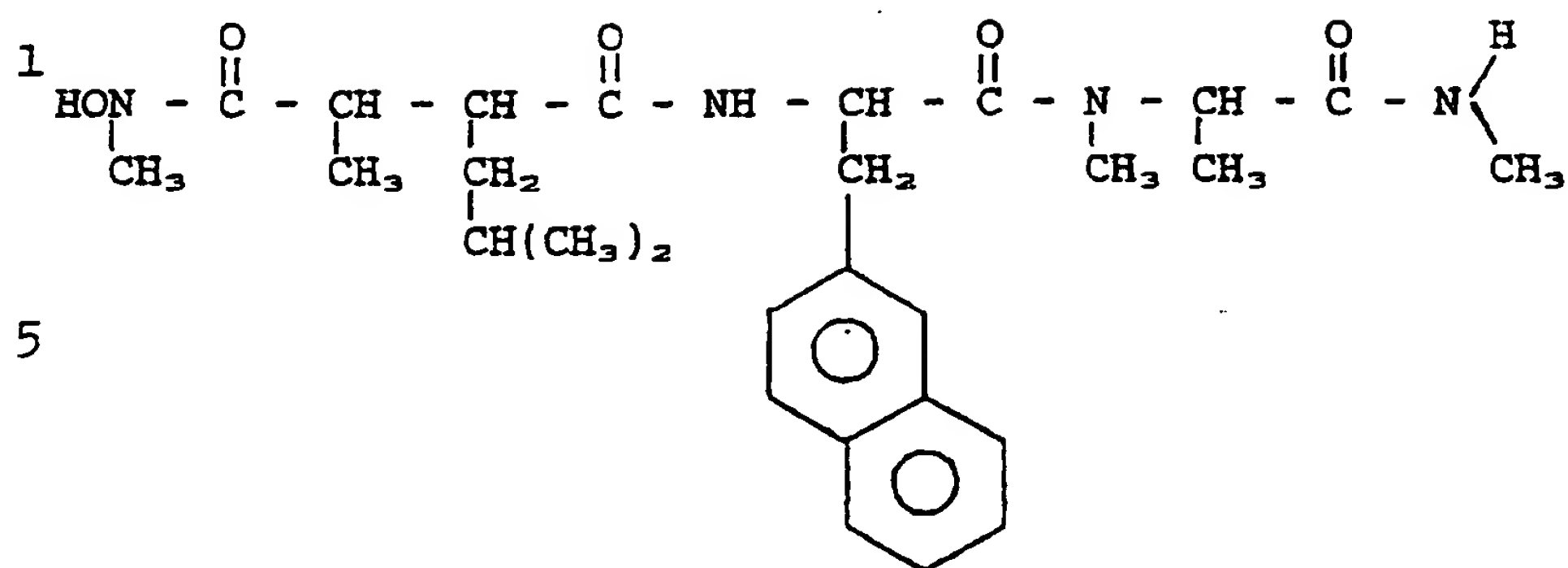


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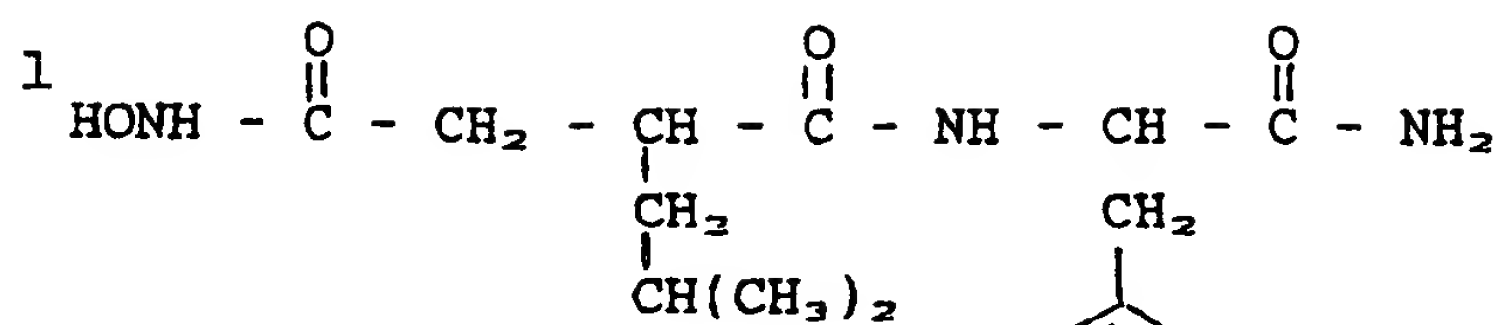
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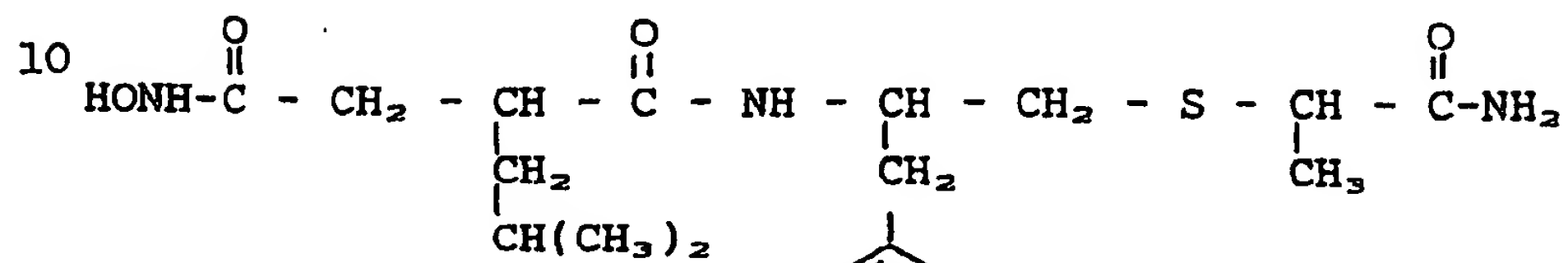
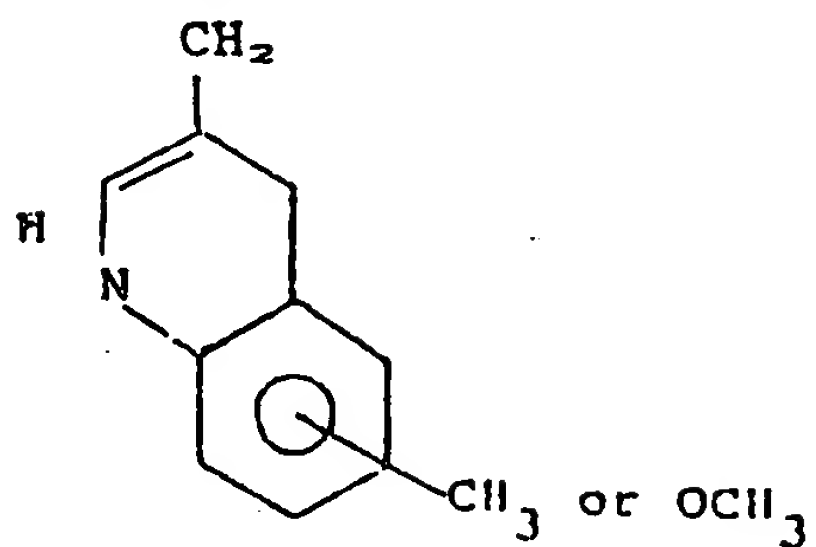
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d.

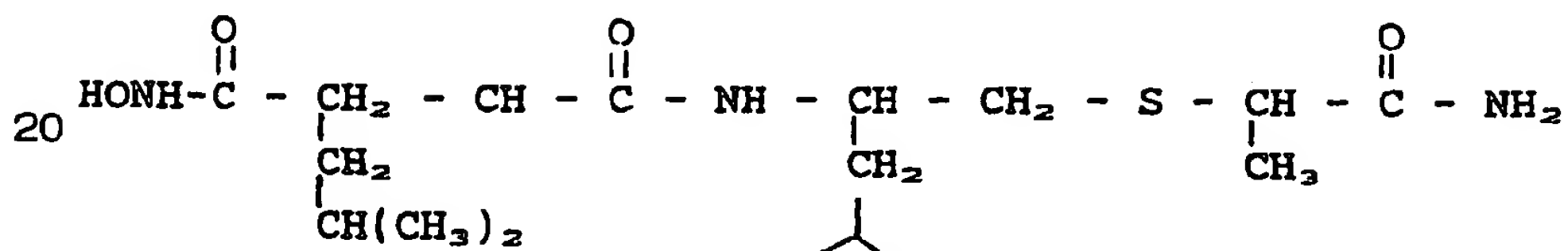
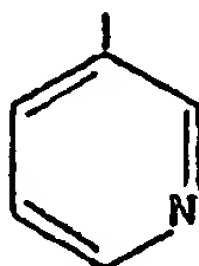
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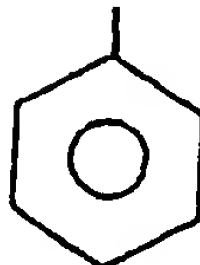
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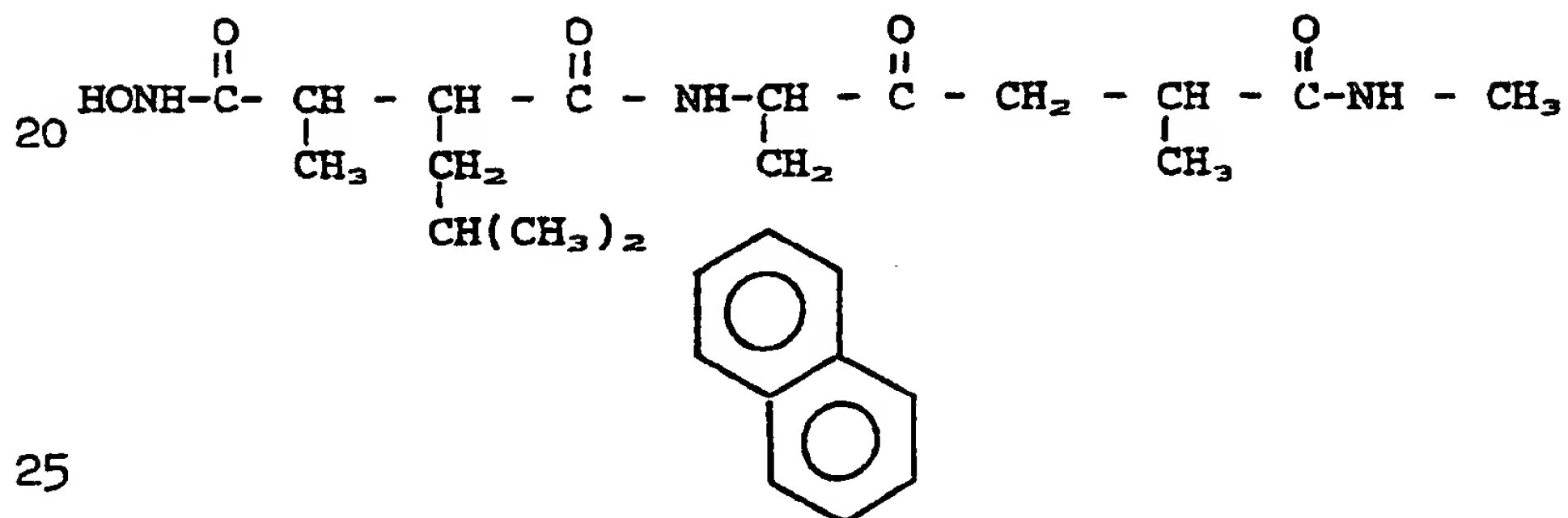
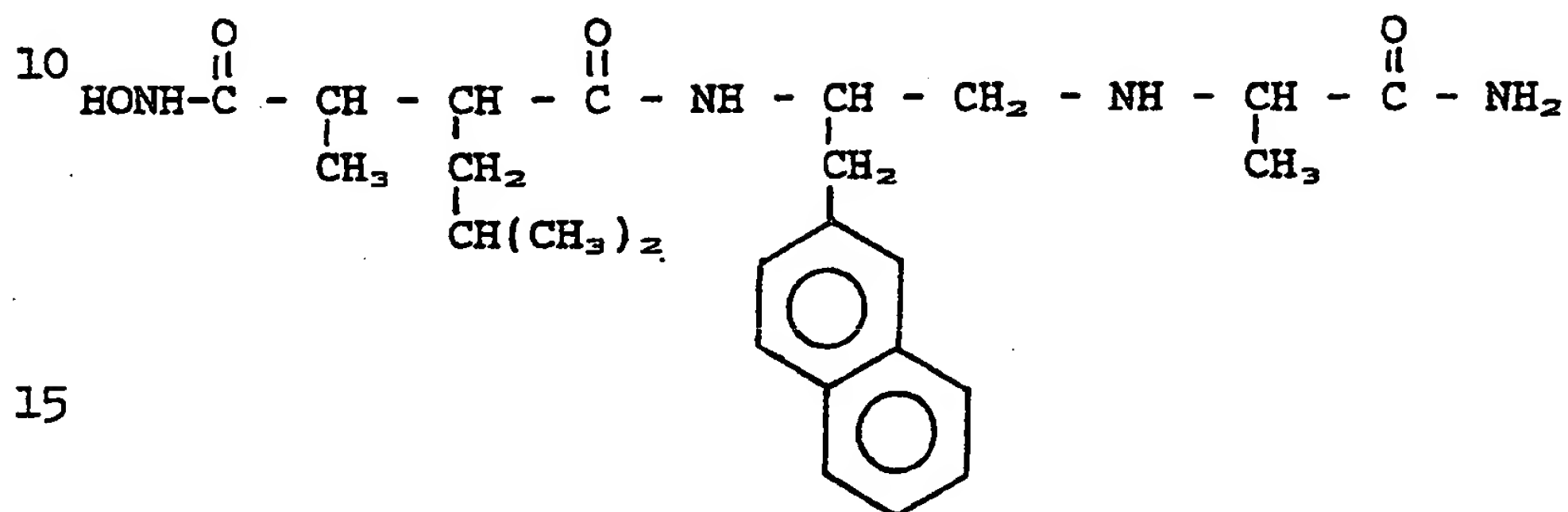
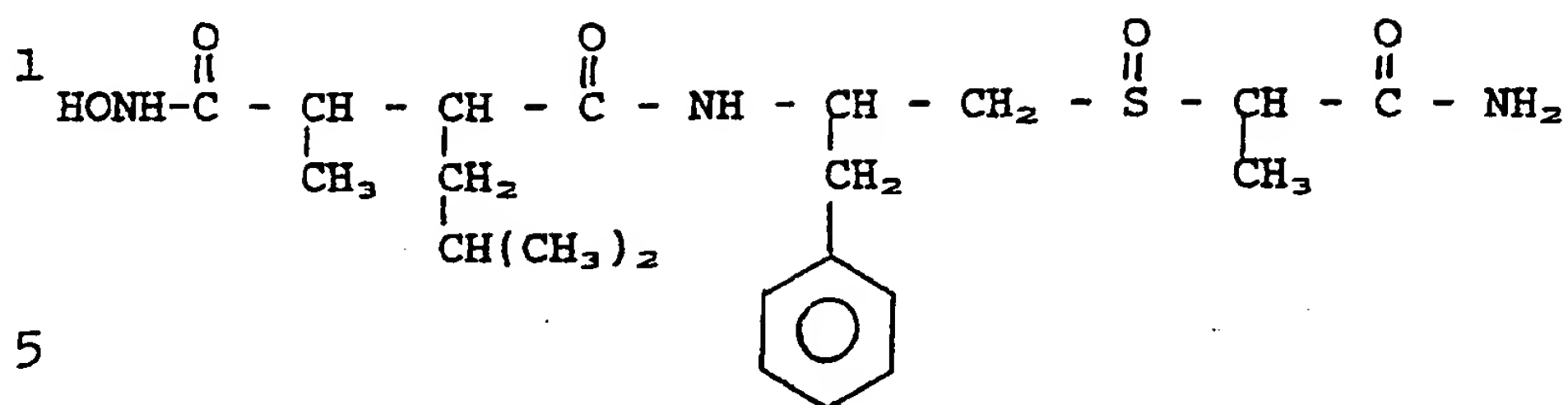


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1 The compounds of the present invention are
inhibitors of mammalian collagenase. They are believed
to bind to mammalian collagenase. More specifically,
they are believed to bind to the active metal, i.e.,
5 zinc in collagenase.

The compounds of the present invention are
inhibitors of collagenase. The effectiveness of a
compound's inhibition by collagenase is shown by the
following assay:

10 Assay Procedures:

Porcine synovial collagenase activity (PSC)
was measured with type I collagen essentially as
described by Darlak et al. (1990). Varying amounts of
inhibitor were added to the acid-soluble calf skin
collagen (0.8 μ M) at 35°C in 0.05 M tris-HCl, 0.2M NaCl,
15 5mM CaCl₂, 0.25 M glucose, pH 7.7. Collagen degradation
was initiated by adding purified porcine synovial
collagenase and the reactions were stopped by the
addition of an equal volume of sample dilution buffer
(Laemmli, 1970) followed by boiling for 2-3 min.
20 Undegraded collagen was resolved from its degradation
products by polyacrylamide slab gel electrophoresis as
described by Laemmli (1970). The gels were fixed in
isopropanol/acetic acid/water (100:40:300 v/v) and then
stained with 1% Coomassie Blue R-250 in fixing solution.
25 After destaining, the percentage of α 1 chain converted
to the corresponding TC fragment was estimated by
densitometry using a Bio-Rad model 610 video
densitometer. IC50 values were estimated from the
dependence of the percent of collagen degraded on
30 inhibitor concentration.

Recombinant human fibroblast collagenase
(rHFC) and porcine synovial gelatinase (PSG) were

1 assayed at 37°C by the procedure of Stack and Gray
2 (1989). The fluorogenic
3 metalloproteinase substrate Dnp-Pro-Leu-Gly-Leu-Trp-Ala-
4 D-Arg-NH₂ was dissolved at an initial concentration of
5 10μM in 0.05 M tris-HCl, 0.2 M NaCl, 5 mM CaCl₂, pH 7.7.
6 Hydrolysis of the substrate at the Gly-Leu bond results
7 in an increase in fluorescence that was monitored using
8 an SLM-500C spectrofluorometer with excitation at 280 nm
9 and emission at 346 nm. The reaction was initiated by
10 addition of the enzyme; after determining the initial
11 rate of substrate hydrolysis an aliquot of inhibitor was
12 added and the inhibited rate redetermined. For lower
13 affinity inhibitors ($IC_{50} \gg [E_0]$, where E_0 is the enzyme
14 concentration), inhibitor potencies were determined from
15 plots of $\log (A_0/A_i - 1)$ vs. $\log [\text{Inhibitor}]$, where A_0 is
16 the activity measured in the absence of inhibitor and A_i
17 is that measured in the presence of inhibitor at
18 concentration i (Ambrose et al., 1950). For high
19 affinity inhibitors ($IC_{50} = [E_0]$) only an upper limit of
20 inhibitor potency could be estimated (Dixon and Webb,
21 1979).

Ambrose, J.F. Kistiakowski, G.B., and Kridl, A.G. (1950)
J. Am. Chem. Soc. 72, 317-321.

25 Darlak, K., Miller, R.B., Stack, M.S., Spatola, A.F.,
and Gray, R.D. (1990) J. Biol. Chem. 265,
5199-5205.

Dixon, M., and Webb, E.C. (1979) Enzymes, Third Edition,
New York, Academic Press, pp.361-368.

30 Laemmli, U.K. (1970) Nature (London) 227, 680-685.
Stack, M.S., and Gray, R.D. (1989) J. Biol.
Chem. 264, 4277-4281.

¹ The results are indicated in the table
hereinbelow.

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TABLE I
Inhibition of MMPs by hydroxamic acid derivatives
P₁ - P₂ - P₃

| IC ₅₀ (μM) | | | | | | | |
|-----------------------|----------------------------------|------------------------|---------------------|--------------------|---------------|-----------------|---------------|
| 0 | P ₁ ' | P ₁ ' | P ₁ ' | PSC/CSC | PSC/FS-7 | PSG/FS-7 | SBFC/FS-7 |
| 1 | Hψ[ONHCO]-DL-Leu | Phe-NH ₂ | | | 250 | 700 | |
| 2 | | Trp-NH ₂ | | | 180 | 370 | |
| 3 | | Phe | Ala-NH ₂ | | 60 | | |
| 4 | | Trp | Ala-NH ₂ | | 60 | | |
| 5 | | Nal | Ala-NH ₂ | | 25-30 | 21 | |
| 6 | | Nal-NH ₂ | | 100-300 30-100 | 350 71 | | |
| 7 | | 1'-Nal-NH ₂ | | 300-500 300-500 | 280 280 | | |
| 8 | Hψ[ONHCOCH ₃]-DL-Leu | Trp-NH ₂ | | | | <0.0001 0.5 | 0.0023 2.2 |
| 9 | | Nal | Ala-NH ₂ | 0.017 0.46 | 0.005 0.45 | <0.0001 0.16 | |
| 10 | | Trp | Ala-NH ₂ | 0.001 0.5 | 0.006 0.24 | 0.002 0.17 | |

TABLE I (con't)

| | | | | | | | | |
|----|---|--|------------------------|-----------------------|----------------------------------|-------------|---------------------------|---------------------------|
| 11 | | | pClPho | Ala-NH ₂ | | | 0.07 4.5 | 0.14 2.5 |
| 12 | | | NaI | Pro-NH ₂ | 0.01--0.03 1-3 | 1.1 | 0.0032 0.1 | 0.032 1.6 |
| 13 | | | NaI | Ala-NH ₂ | 0.01--0.03 0.1-0.3 | | | |
| 14 | | | Dopa(OMe) ₂ | Ala-NH ₂ | 0.03-0.1 1-3 | 0.01 2.8 | 0.004 1.3 | |
| 15 | | | NaI | Ala-NHCH ₃ | | | <0.001 0.028 | 0.016 1.0 |
| 16 | Hψ[ONHCOCH(CH ₃)]-DL-Leu | | Phe | Ala-NH ₂ | 1 >3 | | 10 13 | 10 17 |
| 17 | | | NaI | Ala-NH ₂ | 0.1-0.3 0.1-0.3 0.1 0.3 | | 0.3 0.6 0.4 0.45 | 0.35 0.4 0.6 2.0 |
| 18 | | | Trp | Ala-NH ₂ | 0.3 0.1 0.3 | | 0.1 0.7 0.5 | 0.18 0.46 0.7 |
| 19 | Hψ[ON(CH ₃)COCH ₃]-DL-Leu | | Phe | Ala-NH ₂ | 10-30 300-500 | | | |

*Where more than one IC₅₀ value is shown, the first is for the diastereomer of higher mobility on a C10 reversed phase column and the second is for the diastereomer of lower mobility. For compounds 16-19, there are five asymmetric centers and therefore four isomers. For 16, two of these were resolved; for 18, three isomers were resolved. Where a range of IC₅₀ values is given, 500 inhibition was between the indicated values. Abbreviations: PSC = pig synovial collagenase; CSC = calf skin collagenase; SSC = shark skin collagenase; HSC = human fibroblast collagenase; rHSC = recombinant human fibroblast collagenase; DnPLGLWA-D-R-NH₂. Assays utilizing collagen were carried out as described in Darlak, K., Miller, R.B., Stack, M.S., Spatola, A.F., Gray, R.D. (1990) J. Biol. Chem. 265, 9199-9205; assays utilizing FS-7 were carried out as described in Stack, M.S., Gray, R.D. (1989) J. Biol. Chem. 264, 4277-4281. A "blank" entry indicates that the compound was not assayed.

1 The above preferred embodiments and examples
are given to illustrate the scope and spirit of the
present invention. These embodiments and examples will
make apparent, to those skilled in the art, other
5 embodiments and examples. These other embodiments and
examples are within the contemplation of the present
invention. Therefore, the present invention should be
limited only by the appended claims.

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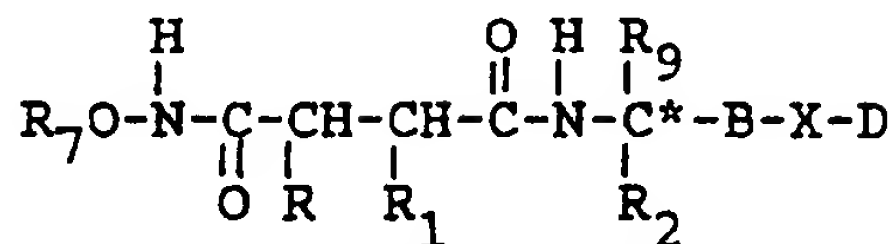
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1 WHAT IS CLAIMED IS:

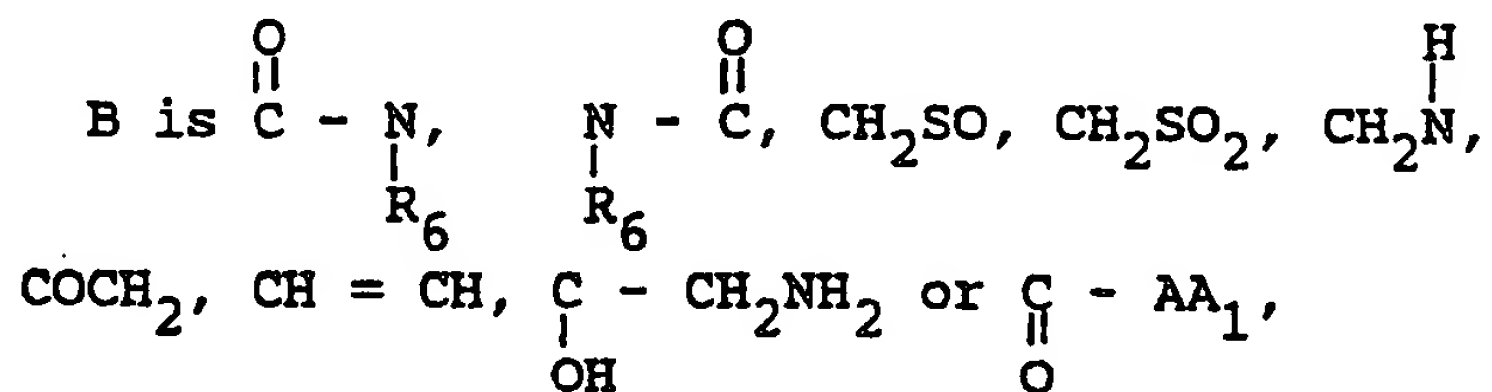
1. A compound of the formula



5 or pharmaceutically acceptable salts thereof

wherein R and R₁ are independently hydrogen,
lower alkyl, aryl or aryl lower alkyl,

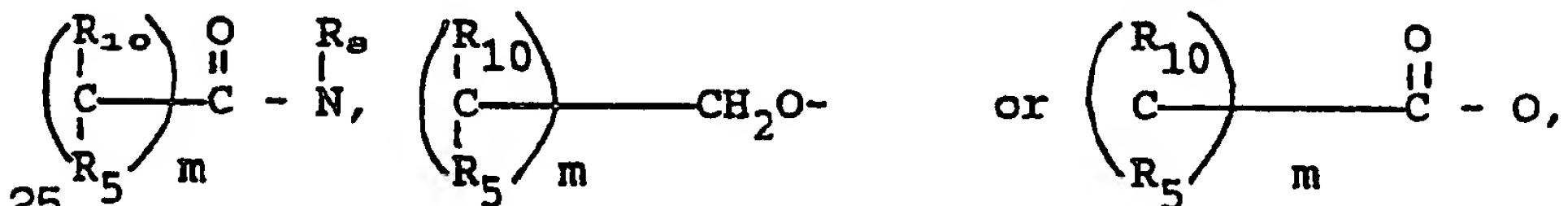
R₂ is aryl lower alkyl or heterocyclic lower
alkyl, said R₂ being unsubstituted or mono- or di-
10 substituted with fluoro, chloro, bromo, halo, nitro,
carboxy, lower carbalkoxy, cyano, lower alkanoyl,
trifloromethyl lower alkyl, hydroxy, lower alkoxy,
formyl, amino, lower alkyl amino, di-lower alkyl amino,
15 mercapto, lower alkylthio or mercapto lower alkyl,



20

AA is an amino acid residue,

X is a chemical bond, lower alkylene,



25

R₉ and R₁₀ are independently hydrogen, methyl
or ethyl,

D, R₅, R₆, R₇ and R₈ are independently
hydrogen or lower alkyl,

m is 1, 2 or 3 with the proviso that when B is
30 $\begin{array}{c} \text{C}-\text{N} \\ || \quad | \\ \text{O} \quad \text{H} \end{array}$, and X is a chemical bond or lower alkylene, then R₂

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1 is not unsubstituted benzyl or benzyl monosubstituted
 with hydroxy, or lower alkoxy and with the further
 proviso that when B is $\begin{array}{c} \text{C-N} \\ || \quad | \\ \text{O} \quad \text{H} \end{array}$ or $\begin{array}{c} \text{C-AA}_1 \\ || \\ \text{O} \end{array}$, and X is $\begin{array}{c} \text{CH-C-N} \\ | \quad || \quad | \\ \text{R}_5 \quad \text{O} \quad \text{R}_6 \end{array}$,

5 then R₂ is not unsubstituted indole or imidazole or
 unsubstituted benzyl or benzyl substituted with hydroxy
 or lower alkoxy.

2. The compound according to Claim 1 wherein

10 B is CH₂S, CH₂SO, $\begin{array}{c} \text{H} \\ | \\ \text{CH}_2\text{N} \end{array}$, CH₂SO₂, $\begin{array}{c} \text{O} \\ || \\ \text{C-AA}_1 \end{array}$, $\begin{array}{c} \text{O} \quad \text{H} \\ || \quad | \\ \text{C-N} \end{array}$, $\begin{array}{c} \text{O} \\ || \\ \text{NH-C} \end{array}$, or
 COCH₂.

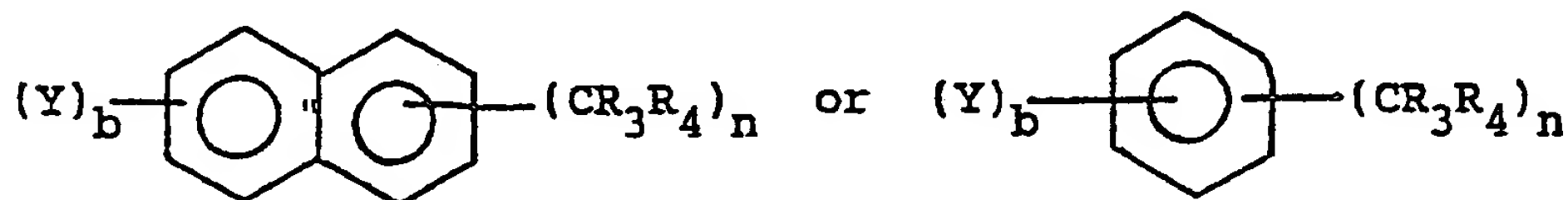
3. The compound according to Claim 2 in which
 B is CH₂S, CH₂SO, CH₂NH, or CH₂SO₂.

4. The compound according to Claim 2 in which

15 B is CH₂S, CH₂SO, CH₂NH, CH₂SO₂, $\begin{array}{c} \text{H} \\ | \\ \text{C-N} \\ || \\ \text{O} \end{array}$ or $\begin{array}{c} \text{C-AA}_1 \\ || \\ \text{O} \end{array}$.

5. The compound according to Claim 1 in which
 R₂ is unsubstituted or substituted

20



25 wherein R₃ and R₄ are independently hydrogen or lower
 alkyl and n is 1-3 and Y is hydrogen lower alkyl or
 lower alkoxy and n is 1 or 2.

6. The compound according to Claim 5 in which
 n is 1 and R₂ and R₄ are hydrogen.

30 7. The compound according to Claim 1 in which
 R₂ is unsubstituted or substituted $(CR_3R_4)_n$ -
 heterocyclic, wherein R₂ and R₃ are independently
 hydrogen or lower alkyl and n is 1-3.

35

1 8. The compound according to Claim 1 in which
 R_3 and R_4 are hydrogen and n is 1.

9. The compound according to Claim 7 in which
 heterocyclic is quinolyl, isoquinolyl, pyridyl or
 5 pyrolyl.

10. The compound according to Claim 9 in
 which heterocyclic is pyridyl.

11. The compound according to Claim 10 in
 which heterocyclic is 2-, 3-, or 4-pyridyl.

10 12. The compound according to Claim 1 in
 which R_7 is hydrogen.

13. The compound according to Claim 1 in
 which R is hydrogen or methyl.

14. The compound according to Claim 1 in
 15 which R_1 is isobutyl or sec-butyl.

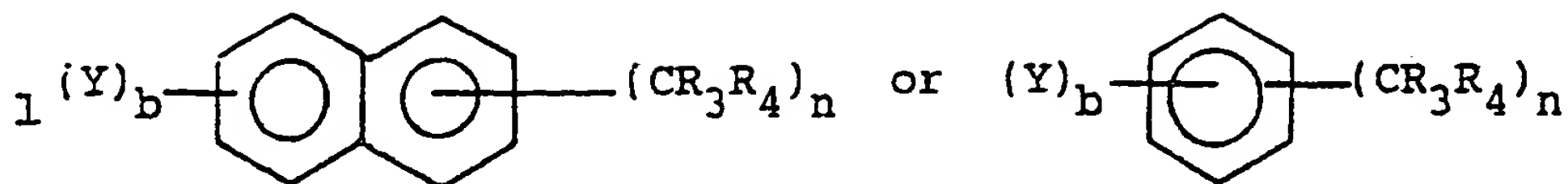
15 15. The compound according to Claim 1 in
 which X-D is $\begin{pmatrix} \text{CH} \\ R_5 \end{pmatrix}_m - \text{C}(=\text{O})\text{NH}_2$.

16. The compound according to Claim 12 in
 20 which B is CH_2S , CH_2SO , $\text{CH}_2\overset{\text{H}}{\underset{|}{\text{N}}}$, CH_2SO_2 , $\text{C}(=\text{O})\text{AA}_1$, $\text{C}(=\text{O})\overset{\text{O}}{\underset{|}{\text{N}}}\overset{\text{H}}{\underset{|}{\text{N}}}$, $\text{NH}-\text{C}(=\text{O})$,
 or COCH_2 .

17. The compound according to Claim 15 in
 25 which B is CH_2S , CH_2SO , CH_2NH or CH_2SO_2 .

18. The compound according to Claim 12 in
 which B is CH_2S , CH_2SO , CH_2NH , CH_2SO_2 , $\text{C}(=\text{O})\overset{\text{H}}{\underset{|}{\text{N}}}$ or $\text{C}(=\text{O})\text{AA}_1$.

19. The compound according to Claim 12 in
 30 which R_2 is unsubstituted or substituted



wherein R_3 and R_4 are independently hydrogen or lower alkyl and n is 1-3 and Y is hydrogen lower alkyl or lower alkoxy and n is 1 or 2.

20. The compound according to Claim 19 in which n is 1 and R_2 and R_4 are hydrogen.

21. The compound according to Claim 12 in which R_2 is unsubstituted or substituted $(\text{CR}_3\text{R}_4)_n$ -heterocyclic, wherein R_2 and R_3 are independently hydrogen or lower alkyl and n is 1-3.

22. The compound according to Claim 21 in which R_3 and R_4 are hydrogen and n is 1.

23. The compound according to Claim 21 in which heterocyclic is quinolyl, isoquinolyl, indolyl, pyridyl or pyrrolyl.

24. The compound according to Claim 23 in which heterocyclic is pyridyl.

25. The compound according to Claim 24 in which heterocyclic is 2-, 3-, or 4-pyridyl.

26. The compound according to Claim 12 in which R is hydrogen or methyl.

27. The compound according to Claim 12 in which R_1 is isobutyl or sec-butyl.

28. The compound according to Claim 12 in which X-D is $\left(\begin{array}{c} \text{CH} \\ \text{R}_5 \end{array} \right)_m - \text{C} \begin{array}{c} \text{NH}_2 \\ || \\ \text{O} \end{array}$.

29. The compound according to Claim 12 in which R is hydrogen or methyl and R_1 is isobutyl.

1 30. The compound according to Claim 29

wherein B is CH_2S , CH_2SO , CH_2N , CH_2SO_2 , $\text{C}(\text{O})\text{AA}_1$, $\text{C}(\text{O})\text{N}(\text{H})$,
 5 $\text{NH}-\text{C}(\text{O})$, or COCH_2 .

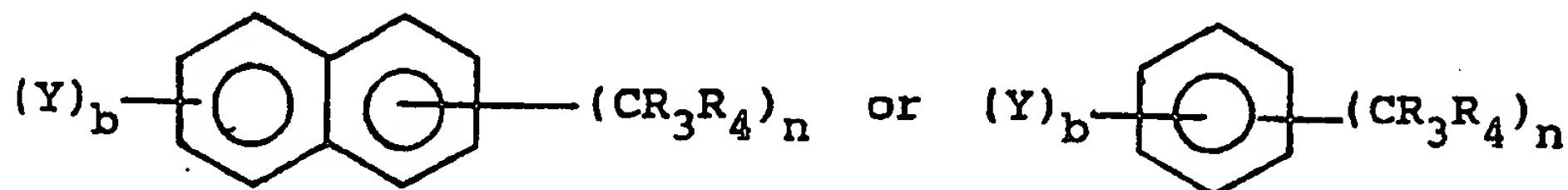
31. The compound according to Claim 30 in which B is CH_2S , CH_2SO , CH_2NH or CH_2SO_2 .

32. The compound according to Claim 31 in

10 which B is CH_2S , CH_2SO , CH_2NH , CH_2SO_2 , $\text{C}(\text{O})\text{N}(\text{H})$ or $\text{C}(\text{O})\text{AA}_1$.

33. The compound according to Claim 29 in which R_2 is unsubstituted or substituted

15



20 wherein R_3 and R_4 are independently hydrogen or lower alkyl and n is 1-3 and Y is hydrogen lower alkyl or lower alkoxy and b is 1 or 2.

34. The compound according to Claim 33 in which n is 1 and R_2 and R_4 are hydrogen.

25 35. The compound according to Claim 29 in which R_2 is unsubstituted or substituted $(\text{CR}_3\text{R}_4)_n$ -heterocyclic, wherein R_2 and R_3 are independently hydrogen or lower alkyl and n is 1-3.

36. The compound according to Claim 35 in which R_3 and R_4 are hydrogen and n is 1.

30 37. The compound according to Claim 36 in which heterocyclic is quinolyl, isoquinolyl, pyridyl or pyrrolyl.

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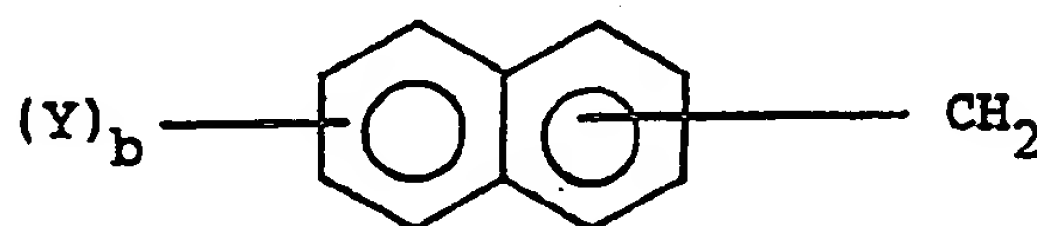
1 38. The compound according to Claim 37 in
which heterocyclic is pyridyl.

39. The compound according to Claim 38 in
which heterocyclic is 2, 3 or 4-pyridyl.

5 40. The compound according to Claim 29 in
which X-D is $\begin{pmatrix} \text{CH} \\ \text{R}_5 \end{pmatrix}_m \text{---} \text{C} \begin{matrix} \text{NH}_2 \\ \parallel \\ \text{O} \end{matrix}$.

41. The compound according to Claim 1 in
which R_7 is hydrogen, and R_2 is

10

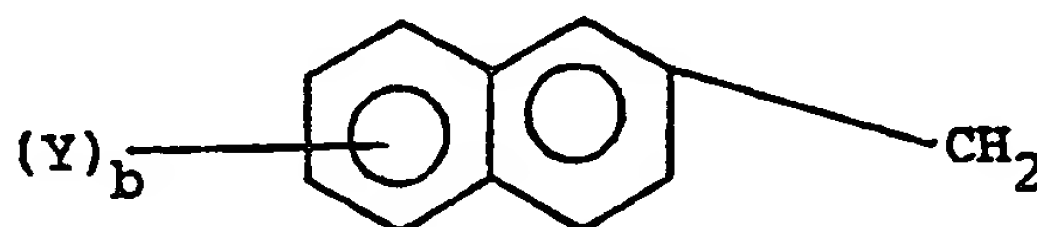


15 wherein Y is hydrogen, halo, nitro, carboxy, lower
carbalkoxy, cyano, lower alkanoyl, trifluoromethyl,
lower alkyl, hydroxy, lower alkoxy, formyl, amino, lower
alkyl amino, di-lower alkylamino, mercapto, lower
alkylthio or mercapto lower alkyl and b is 1 or 2.

20 42. The compound according to Claim 41 in
which R_2 is hydrogen or lower alkyl and b is 1.

43. The compound according to Claim 41 in
which R_2 is

25



44. The compound according to Claim 41 in

30 which B is CH_2S , CH_2SO , $\text{CH}_2\overset{\text{H}}{\underset{|}{\text{N}}}$, CH_2SO_2 , $\text{C} \begin{matrix} \parallel \\ \text{O} \end{matrix} \text{---} \text{AA}_1$, $\text{C} \begin{matrix} \text{H} \\ | \\ \parallel \\ \text{O} \end{matrix} \text{---} \text{N}$, $\text{NH} \text{---} \text{C} \begin{matrix} \parallel \\ \text{O} \end{matrix}$,
or COCH_2 .

35

1 45. The compound according to Claim 44 in
which B is CH_2S , CH_2SO , CH_2NH or CH_2SO_2 .

46. The compound according to Claim 41 in
5 which B is CH_2S , CH_2SO , CH_2NH , CH_2SO_2 , $\text{C}(\text{H})=\text{N}$ or $\text{C}(\text{H})=\text{AA}_1$.

47. The compound according to Claim 41 in
which R is hydrogen or methyl.

48. The compound according to Claim 41 in
10 which R_1 is isobutyl or sec-butyl.

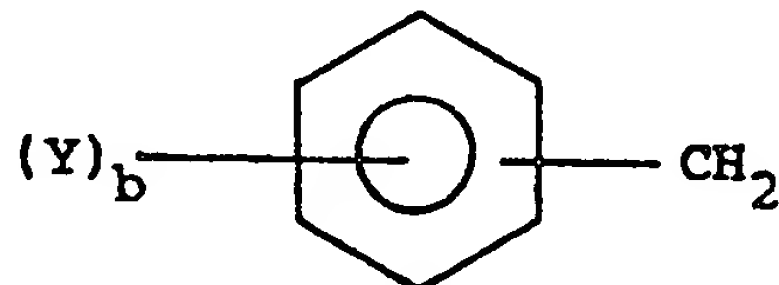
49. The compound according to Claim 41 in
which X-D is $\left(\text{CH}(\text{R}_5)\right)_m - \text{C}(=\text{O})\text{NH}_2$.

50. The compound according to Claim 41 in
15 which R is hydrogen or methyl, and R_1 is isobutyl.

51. The compound according to Claim 44 in
which R is hydrogen or methyl, and R_1 is isobutyl.

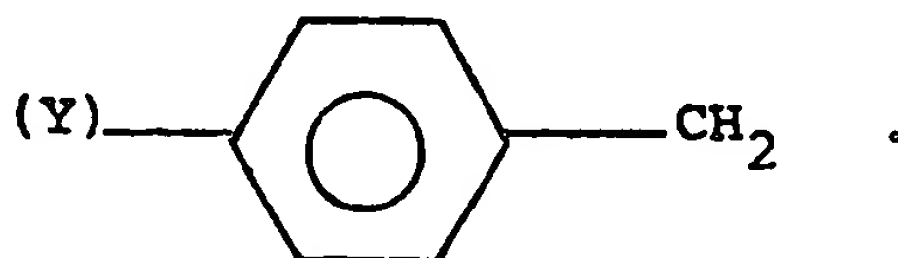
52. The compound according to Claim 46 in
which R is hydrogen or methyl, and R_1 is isobutyl.

53. The compound according to Claim 12 in
20 which R_2 is



25 wherein Y is lower alkyl, halo or lower alkoxy, and b is
1 or 2.

54. The compound according to Claim 53 in
which R_2 is



1 55. the compound according to Claim 53 in
which R_2 is DOPA(OMe)₂.

56. The compound according to Claim 23 in
which R_2 is pyridylmethyl, quinolylmethyl,
5 isoquinolylmethyl or pyrrolmethyl.

57. The compound according to Claim 56 in
which B is CH_2S , CH_2SO , CH_2NH , CH_2SO_2 , $\begin{array}{c} \text{O} \\ \parallel \\ \text{C-AA}_1 \\ \text{O} \end{array}$, $\begin{array}{c} \text{O} \text{ H} \\ \parallel \text{ } | \\ \text{C-N} \end{array}$, $\begin{array}{c} \text{NH-C} \\ \parallel \\ \text{O} \end{array}$,
10 or $COCH_2$.

58. The compound according to Claim 57 in
which B is CH_2S , CH_2SO , CH_2NH or CH_2SO_2 .

59. The compound according to Claim 58 in
15 which B is CH_2S , CH_2SO , CH_2NH , CH_2SO_2 , $\begin{array}{c} \text{H} \\ | \\ \text{C-N} \\ \parallel \\ \text{O} \end{array}$ or $\begin{array}{c} \text{C-AA}_1 \\ \parallel \\ \text{O} \end{array}$.

60. The compound according to Claim 56 in
which R is hydrogen or methyl.

61. The compound according to Claim 56 in
20 which R_1 is isobutyl or sec-butyl.

62. The compound according to Claim 56 in
which R is hydrogen or methyl, and R_1 is isobutyl.

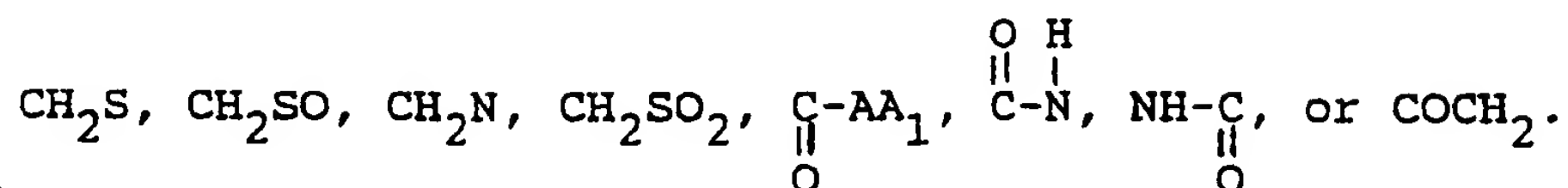
63. The compound according to Claim 56 in
which R_2 is pyridylmethyl.

64. The compound according to Claim 63 in
25 which pyridyl is 2-, 3- or 4-pyridyl.

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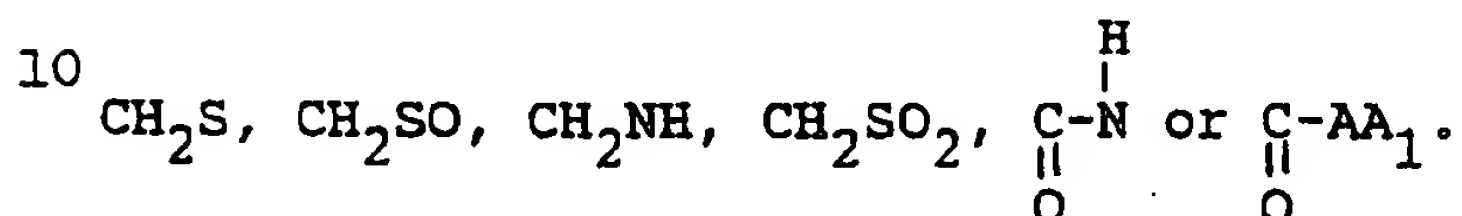
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1 65. The compound according to Claim 63 in
which B is



5 66. The compound according to Claim 63 in
which B is CH_2S , CH_2SO , CH_2NH or CH_2SO_2 .

67. The compound according to Claim 63 in
which B is



68. The compound according to Claim 63 in
which R_9 is methyl or hydrogen.

15 69. The compound according to Claim 63 in
which R is hydrogen or methyl.

70. The compound according to Claim 63 in
which R_1 is isobutyl.

20 71. The compound according to Claim 63 in
which X-D is $\left(\begin{smallmatrix} \text{CH} \\ \text{R}_5 \end{smallmatrix} \right)_m - \text{C}(=\text{O})-\text{NH}_2$.

72. The compound according to Claim 63 in
which R is CH_3 or hydrogen, and R_1 is isobutyl.

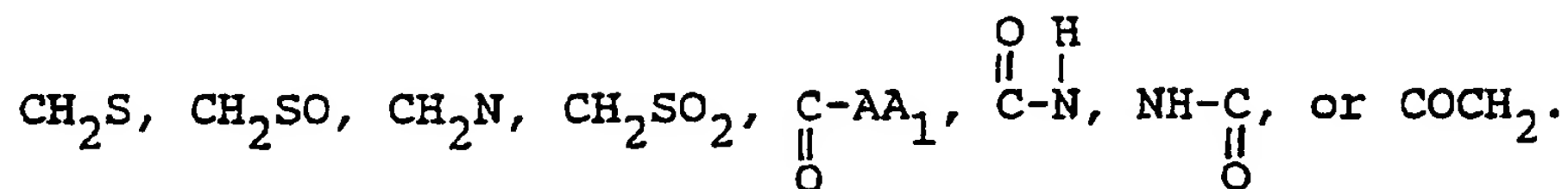
25 73. The compound according to Claim 56 in
which R_2 is indolylmethyl.

74. The compound according to Claim 73 in
which R_2 is unsubstituted or substituted 2- or 3-
indolylmethyl.

30 75. The compound according to Claim 74 in
which R_2 is lower alkyl or lower alkoxy substituted
indolylmethyl.

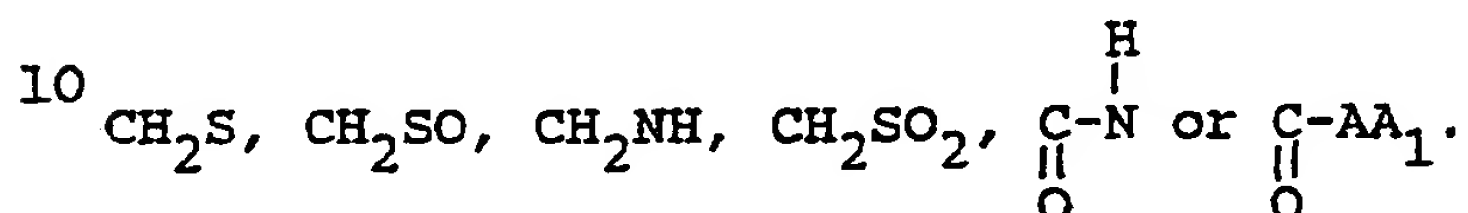
76. The compound according to Claim 75 in
which R_2 is methyl or methoxy substituted indolylmethyl.

1 77. The compound according to Claim 73 in
which B is



5 78. The compound according to Claim 73 in
which B is CH_2S , CH_2SO , CH_2NH or CH_2SO_2 .

79. The compound according to Claim 73 in
which B is



80. The compound according to Claim 73 in
which R is hydrogen or methyl.

15 81. The compound according to Claim 73 in
which R_1 is isobutyl.

82. The compound according to Claim 73 in
which X-D is $\begin{pmatrix} \text{CH} \\ \text{R}_5 \end{pmatrix}_m - \begin{array}{c} \text{C-NH}_2 \\ \parallel \\ \text{O} \end{array}.$

20 83. The compound according to Claim 73 in
which R is hydrogen or methyl, and R_1 is isobutyl.

84. The compound according to Claim 1 having
the configuration around the chiral centers are in the S
or R form.

25 85. The compound according to Claim 1 in
which the configuration around the asterisked carbon is
S.

86. The compound according to Claim 1 which
is $\text{HONH}-\begin{array}{c} \text{C} \\ \parallel \\ \text{O} \end{array}-\text{CH}_2\text{CH}(\text{CH}_2\text{CH}(\text{CH}_3)_2)-\text{CO-Nal-Ala-NH}_2.$

30 87. The compound according to Claim 1 which
is $\text{HO-NH-CO-CH}_2-\text{CH}-(\text{CH}_2-\text{CH}(\text{CH}_3)_2)-\text{CO-Nal-Pro-NH}_2.$

1 88. The compound according to Claim 1 which
is $\text{HO-NH-CO-CH}(\text{CH}_3)\text{-CH}(\text{CH}_2\text{-CH}(\text{CH}_3)_2)\text{-CO-Nal-Ala-NH}_2$.

89. The compound according to Claim 1 which

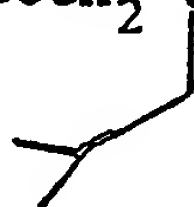
5 is $\text{HON-COCH}_2\text{-CH-CO-Pal-Ala-NH}_2$, wherein Pal is 3-



pyridylalanine.

10 90. The compound according to Claim 1 which

is $\text{HON-COCH}_2\text{-CH-CO-Nal (CH}_2\text{S)Ala-NH}_2$.

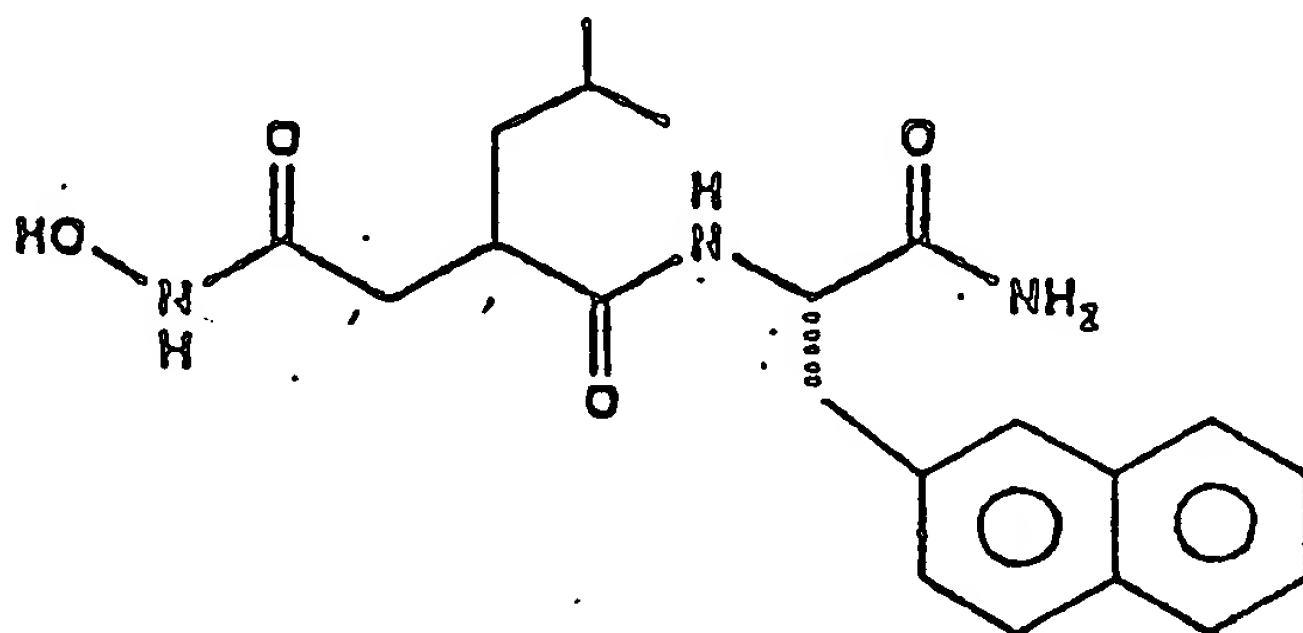


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91. The compound according to Claim 1 which
is $\text{HO-NH-CO-CH}_2\text{-CH}(\text{CH}_2\text{CH}(\text{CH}_3)_2)\text{-CONal-(CH}_2\text{NH)-Ala-NH}_2$.

92. The compound according to Claim 1 having
the formula

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1 97. A method of treating a mammalian
collagenase-related disorder which comprises
administering to a mammal in need of treatment an
inhibitory effective amount of a compound of Claim 1.

5 98. The method of Claim 97 wherein said
mammalian collagenase-related disorder is rheumatoid
arthritis.

 99. The method of Claim 97 wherein said
mammalian collagenase-related disorder is periodontal
10 disease.

 100. The method of Claim 97 wherein said
mammalian collagenase-related disorder is corneal
ulceration.

 101. The method of Claim 100 wherein said
15 corneal ulceration is the result of alkali burning of
the cornea.

 102. The method of Claim 100 wherein corneal
ulceration is the result of said infectious keratitis.

 103. The method of Claim 102 wherein said
20 infectious keratitis is induced by infection by
Pseudomonas aeruginosa.

 104. The method of Claim 97 wherein said
mammalian collagenase-related disorder is tumor
metastasis.

25 105. A method of treating corneal ulceration
resulting from infectious keratitis induced by infection
by Pseudomonas aeruginosa comprising administering a
corneal ulceration inhibiting amount of the compound of
Claim 1 to a mammal suffering from cornea ulceration
resulting from infectious keratitis caused by infection
30 by Pseudomonas aeruginosa.

 106. A method of treating corneal ulceration
resulting from alkali burning of the cornea comprising

1 administering a cornea ulceration inhibiting amount of
the compound of Claim 1 to a mammal suffering from
corneal ulceration resulting from alkali burning of the
cornea.

5 107. The method according to Claim 97 in
which the collagenase related disorder is dermatitis.

108. The compound according to Claim 12 in
which B is CH_2S , CH_2SO , CH_2SO_2 , CH_2NH , COCH_2 , $\text{CH}=\text{CH}$ or
 $\text{CH}-\text{CH}_2\text{NH}_2$.

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109. The compound according to Claim 108 in
which R_2 is heterocyclic lower alkyl.

110. The compound according to Claim 109 in
which R_2 is quinolylmethyl, isoquinolylmethyl,
indolylmethyl, pyridylmethyl or pyrrolmethyl.

15 111. The compound according to Claim 110 in
which R_2 is pyridylmethyl or indolylmethyl.

112. The compound according to Claim 111 in
which R_2 is 2-, 3- or 4-pyridyl methyl or 3-
indolylmethyl.

20 113. The compound according to Claim 109 in

which B is CH_2S , CH_2SO , CH_2SO_2 or $\text{CH}_2\overset{\text{H}}{\underset{|}{\text{N}}}$.

25 114. The compound according to Claim 110 in
which R_2 is hydrogen or methyl.

115. The compound according to Claim 110 in
which R_1 is isobutyl or sec-butyl and R is hydrogen or
methyl.

116. The compound according to Claim 108 in
which B is naphthylalanine methyl or DOPA.

30 117. The compound according to Claim 116 in
which B is CH_2S , CH_2SO , CH_2SO_2 , or CH_2NH .

118. The compound according to Claim 110 in
 1 which R is hydrogen or methyl.

119. The compound according to Claim 110 in
 which R₁ is isobutyl or sec-butyl and R is hydrogen or
 5 methyl.

120. The compound according to Claim 12 in
 which B is $\begin{array}{c} \text{H} \quad \text{H} \\ | \quad | \\ \text{C} - \text{N}, \text{N} - \text{C} \\ || \quad || \\ \text{O} \quad \text{O} \end{array}$, X is a chemical bond or lower
 10 alkylene and R₂ is heterocyclic lower alkyl.

121. The compound according to Claim 120 in
 which R₂ is quinolylmethyl, isoquinolylmethyl,
 indolylmethyl, pyridylmethyl, and pyrrolylmethyl.

122. The compound according to Claim 120 in
 15 which R₂ is pyridylmethyl or indolylmethyl.

123. The compound according to Claim 120 in
 which R₂ is 2-, 3-, or 4-pyridylmethyl or 3-
 indolylmethyl.

124. The compound according to Claim 12 in
 20 which B is $\begin{array}{c} \text{H} \\ | \\ \text{C} - \text{N} \\ || \quad | \\ \text{O} \quad \text{H} \end{array}$, $\begin{array}{c} \text{H} \\ | \\ \text{N} - \text{C} \\ || \\ \text{O} \end{array}$ and X is chemical bond and R₂
 is naphthylalanine or DOPA.

125. The compound according to Claim 12 in
 25 which B is $\begin{array}{c} \text{H} \\ | \\ \text{C} - \text{N} \\ || \quad | \\ \text{O} \quad \text{H} \end{array}$, or $\begin{array}{c} \text{O} \\ || \\ \text{C} - \text{AA}_1 \end{array}$, X is $\begin{array}{c} \text{H} \\ | \\ \text{CH} - \text{C} - \text{N} \\ | \quad || \\ \text{R}_5 \quad \text{O} \end{array}$, and
 R₂ is naphthylalanine or DOPA.

126. The compound according to Claim 12 in
 30 which B is $\begin{array}{c} \text{H} \\ | \\ \text{C} - \text{N} \\ || \quad | \\ \text{O} \quad \text{H} \end{array}$ or $\begin{array}{c} \text{O} \\ || \\ \text{C} - \text{AA}_1 \end{array}$, X is $\begin{array}{c} \text{H} \\ | \\ \text{CH} - \text{C} - \text{NH} \\ | \quad || \\ \text{R}_5 \quad \text{O} \end{array}$ and
 R₂ is heterocyclic lower alkyl.

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127. The compound according to claim 126 in which R_2 is pyridylmethyl, quinolylmethyl, pyrrollylmethyl, or isopropylmethyl. 128. The compound according to claim 125 in which R_2 is pyridyl methyl. 129. The compound according to claim 127 in which R_2 is naphthylalanine. 130. The pharmaceutical composition for the treatment of a mammalian collagenase related disorder which comprises a pharmaceutically effective amount of a compound according to claim 108 and a pharmaceutically acceptable carrier therefor. 131. The pharmaceutical composition for the treatment of a mammalian collagenase related disorder which comprises a pharmaceutically effective amount of a compound according to claim 116 and a pharmaceutically acceptable carrier therefor. 132. The pharmaceutical composition for the treatment of a mammalian collagenase related disorder which comprises a pharmaceutically effective amount of a compound according to claim 120 and a pharmaceutically acceptable carrier therefor. 133. The pharmaceutical composition for the treatment of mammalian collagenase related disorder which comprises a pharmaceutically effective amount of a compound according to claim 124 and a pharmaceutically acceptable carrier thereof. 134. The pharmaceutical composition for the treatment of a mammalian collagenase related disorder which comprises a pharmaceutically effective amount of a compound according to claim 125 and a pharmaceutically acceptable carrier therefor.

1 135. The pharmaceutical composition for the
treatment of a mammalian collagenase related disorder
which comprises a pharmaceutically effective amount of a
compound according to Claim 126 and a pharmaceutically
5 acceptable carrier thereof.

10 136. A method of treating a mammalian
collagenase related disorder in a mammal which comprises
administering to a mammal in need of such treatment an
inhibiting effective amount of a compound according to
Claim 108.

15 137. A method of treating a mammalian
collagenase related disorder in a mammal which comprises
administering to a mammal in need of such treatment an
inhibiting effective amount of a compound according to
Claim 116.

20 138. A method of treating a mammalian
collagenase related disorder in a mammal which comprises
administering to a mammal in need of such treatment an
inhibiting effective amount of a compound according to
Claim 120.

25 139. A method of treating a mammalian
collagenase related disorder in a mammal which comprises
administering to a mammal in need of such treatment an
inhibiting effective amount of a compound according to
Claim 124.

30 140. A method of treating a mammalian
collagenase related disorder in a mammal which comprises
administering to a mammal in need of such treatment an
inhibiting effective amount of a compound according to
Claim 125.

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1 141. A method of treating a mammalian
collagenase related disorder in a mammal which comprises
administering to a mammal in need of such treatment an
inhibiting effective amount of a compound according to
5 Claim 126.

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